Bulletin on NARCOTICS

Vol. VIII, No. 1, JANUARY-MARCH 1956

UNITED NATIONS

EUROPEAN OFFICE

Geneva

NOTE

Reproduction of unsigned material is authorized and welcome. For permission to reproduce signed material, request should be made to the Secretariat of the United Nations. It would be appreciated, moreover, if a copy of any publication containing such reproduction were sent to the Secretariat.

* * *

Opinions expressed in signed articles are not necessarily those of organs or Members of the United Nations.

Table of Contents

Page

GENERAL

The Paris Protocol of 1948 1

Development of synthetic narcotic drugs 11

TECHNICAL

The problem of morphine synthesis, by Prof. D. Ginsburg 15

Natural and synthetic drugs with morphine-like effects evaluated from a pharmacognostic point of view, by Prof. A. Nordal 18

Some new analgesics and antispasmodics, by Prof. Dr. G. Ehrhart 28

OFFICIAL

Legal trade in narcotics in 1954 33

Estimated world requirements in narcotic drugs for 1956 35

WHO-Expert Committee on drugs liable to produce addiction—Sixth report 37

BIBLIOGRAPHY

Synthetic drugs 41

The Paris Protocol of 1948 [1]

The principle that *all* addiction-producing substances should be under international control was generally acknowledged nearly forty-five years ago and has rarely been challenged. It has long been agreed that, ideally, the list of drugs under control should, at any given moment, faithfully reflect the preponderance of expert opinion on the addiction liability of established and newly developed drugs.[2] Nevertheless, the task of translating this principle into effective treaty provisions binding upon governments has taken many years, and indeed still goes on. In these efforts, the Paris Protocol of 19 November 1948 occupies a notable place.

Why has it proved so difficult to devise an acceptable procedure for applying a non-controversial principle? The problem arises chiefly from the natural reluctance of governments to undertake obligations of uncertain scope and from the technical difficulty of establishing whether a drug is addiction-producing or not. New addiction-producing drugs are constantly being added to the physician's arsenal of analgesics, and since international conferences cannot remain in permanent session, some other way must be found to determine which new drugs are addiction-producing and to bring them under international control with a minimum of delay. Although there are many ways in which this might be done, governments have gradually been led, by considerations of administrative expediency, to delegate these far-reaching powers to international agencies.

It is only within the context of this larger development that the story of the Paris Protocol may be fully understood. It is proposed, therefore, to give some account of the solutions reached at the international conferences held in 1912, 1925 and 1931, before turning to the chain of events which culminated in the signing of the Paris Protocol during the third session of the General Assembly of the United Nations.

I. The earlier solutions

The Hague Convention

The problem of devising machinery whereby additional drugs might be brought under control at any time was first tackled by the framers of the Hague Convention. They decided that each Party should itself be the judge of which new drugs presented dangers similar to those of morphine or cocaine, and that each judgment should be based on " scientific research, generally recognized ". There was no provision for international action to propose the inclusion of a new drug. Thus the scope of the Convention was limited to a few substances specified by name and to " all new derivatives of morphine, of cocaine, or of their respective salts, and to every other alkaloid of opium, which may be shown by scientific research, generally recognized, to be liable to similar abuse and productive of like ill-effects ".[3]

The shortcomings of this solution are more obvious now than they were in 1912. It was probably not foreseen to what extent new narcotics would be developed and used medically, and that the addiction-producing effects of new drugs would be difficult to determine and sometimes would be established only after extended clinical use. It was also not expected that differences of expert opinion about the addictive nature of a drug might at any rate temporarily exist. The concept of " generally recognized scientific research " was, of course, too vague to be a good basis on which to decide whether or not to control newly developed dangerous drugs.

Article 14 (d) *of the Hague Convention in Operation*

When the treaty came into full operation after the First World War, difficulties arose almost immediately. At its second session, the Assembly of the League of Nations, acting on a request of the representative of France, recommended unanimously that the Advisory Committee on Traffic in Opium and Other Dangerous Drugs " extend their investigations to include not only the drugs mentioned in the Convention of 1912, but also all dangerous drugs of whatever origin which produce similar effects, and to advise as to the desirability of convoking a further international conference . . . with a view to drawing up a convention for the suppression of the abuse of such drugs ". [4]

The Advisory Committee transmitted to governments a list of the drugs mentioned by the French representative, in order to obtain the observations of their health departments, and therefore postponed the question of calling a conference. When the comments had been received, it referred the matter to a mixed sub-committee of the Health Committee and the Advisory Committee " for consideration and report ".[5]

The mixed sub-committee, in due course, recommended that the provisions of the Hague Convention should be extended to four derivatives of ecgonine, but the Advisory

[1] The following abbreviations for the titles of treaties will be utilized : the Protocol bringing under international control drugs outside the scope of the Convention of 13 July 1931 for limiting the manufacture and regulating the distribution of narcotic drugs, as amended by the Protocol signed at Lake Success on 11 December 1946, will be referred to as the " Paris Protocol "; the International Opium Convention signed at The Hague on 23 January 1912, as the " Hague Convention "; the International Opium Convention signed at Geneva on 19 February 1925 as the " 1925 Convention "; the Convention of 13 July 1931 for limiting the manufacture and regulating the distribution of narcotic drugs as the " 1931 Convention "; and the Protocol of 11 December 1946 amending the Agreements, Conventions and Protocols on narcotic drugs concluded at The Hague on 23 January 1912, at Geneva on 11 February 1925 and 19 February 1925 and 13 July 1931, at Bangkok on 27 November 1931 and at Geneva on 26 June 1936, as the " 1946 Protocol ".

[2] Since 1931, it has also been agreed that the list should include, in addition, substances readily convertible into narcotic drugs.

[3] Article 14 (*d*) of the Convention. Contracting Parties agreed to " apply the laws and regulations respecting the manufacture, import, sale or export of morphine, cocaine, and their respective salts " to such drugs.

[4] League of Nations, *Records of the Second Assembly*, Geneva, 1921, p. 541.

[5] Advisory Committee on Traffic in Opium and Other Dangerous Drugs. *Reports to the Council*, Second Session (April 1922), A.15.1922, p. 9, and Fourth Session (January 1923), C.37.1923.IV, p. 4.

Committee merely noted the sub-committee's report and discontinued its participation in the sub-committee's work.[6]

The 1925 Convention

Later in 1924, at the Second Opium Conference, which met at Geneva (November 1924-February 1925), the British Government proposed an important modification in the provisions of the Hague Convention for controlling new drugs—namely, that an international authority (in this case, the Health Committee of the League, after consultation with the Office international d'Hygiène publique) should be empowered to declare that any narcotic drug was " liable to similar abuse and productive of like ill-effects ", as those already under control. Amended so that it would apply only to manufactured drugs, this proposal was adopted by the Conference, and the procedure was gradually filled out so as to provide that, in addition, (i) the Health Committee would recommend that the provisions of the Convention should apply to the drug concerned and would so inform the Council of the League of Nations, which would communicate this recommendation to Parties; (ii) Parties prepared to accept it would notify the Secretary-General, who would inform other Parties, and the Convention would apply to this drug among all Parties accepting the Health Committee's recommendation.[7]

In the meantime, however, the representative of Egypt had proposed to the Conference that the decisions of the Health Committee should be made binding upon all Parties. The response to this proposal had been sharply unfavourable. Some of the comments were : " An unreserved surrender of sovereign authority " . . . " an entirely new precedent, the consequences of which we cannot foresee but which might be most dangerous in the future " . . . " it seems to me impossible for a sovereign State to accept as binding on it some future decision of a body constituted like the Office international d'Hygiène publique, or like any other consultative body, for that matter, without its having been consulted and having concurred in the recommendation made ". The Egyptian proposal was rejected by a vote of 17 to 2.[8]

Article 8 of the 1925 Convention also contained a similar procedure for freeing from control preparations in which narcotic drugs were compounded with other medicaments in such a way that the resulting mixture did not produce addiction. In this instance, however, the Health Committee's decision was final.[9]

Article 10 of the 1925 Convention constituted a considerable improvement over article 14 (d) of the Hague Convention. It set up an international authority to determine which additional drugs should be placed under control; it made it possible to extend the scope of international narcotics control, without formal amendment of the Convention to any narcotic drug " liable to similar abuse and productive of similar ill-effects " as those manufactured drugs designated by the Conference itself. It created machinery whereby Parties were informed of each Health Committee recommendation and of each acceptance by a Party of such a recommendation.

At the same time, experience with the more far-reaching control measures of the 1925 Convention, such as the system of import certificates and export authorizations and the submission to the Permanent Central Opium Board of more detailed statistical data, revealed the need for a procedure by which decisions to place new drugs under international control might be made immediately binding upon all Parties. Administrative problems are apt to arise if the scope of control varies from country to country.

For example, authorities responsible for issuing import certificates and export authorizations would have to know whether or not the system would be in effect *vis-à-vis* another country. Statistical controls might also be rather difficult to apply. What was even more serious, very dangerous drugs might remain uncontrolled in many countries because of official inertia or perhaps even on account of pressure against their control; and in all countries there would be some delay while authorities were weighing what action to take. Furthermore, there was no requirement for placing a new drug, no matter how dangerous it might be and no matter how rapidly unscrupulous manufacturers might be making it, under temporary national or international control during the considerable period required for the Health Committee to consult the Office international and to reach its decision.

The danger of undue delays in placing new drugs under control was dramatically revealed by the case of benzoylmorphine. In 1928 the Advisory Committee learned that this ester of morphine, which did not yet fall within the scope of the Geneva Convention, was being manufactured in large quantities as a substitute for morphine. The need for control was so urgent that although the procedure of article 10 had been invoked, the Advisory Committee felt obliged to adopt a resolution drawing the attention of governments to the immediate necessity of placing the drug under control.[10]

---

[6] Advisory Committee, *Report to the Council*, Sixth Session (August 1924), A.32.1924.XI, p. 3 and Annex 5, p. 22. These derivatives were probably not subject to control under article 14 (*d*) of the Hague Convention on the ground that they had been discovered before 1912 and were thus not " new ". The procedure is nevertheless interesting because this is the first occasion on which an international body was consulted in this connexion and a recommendation was made. A similar procedure was soon to be incorporated in the 1925 Convention.

[7] For the text of the British proposal, see *Records of the Second Opium Conference*, II, p. 291; for the discussions, see *ibid.*, I, 222, 263, 273-5, 284-90, 357-8; II, 290-292, 295-6, 301, 304-5. The text of the final article reads as follows :

" In the event of the Health Committee of the League of Nations, after having submitted the question for advice and report to the Permanent Committee of the Office international d'Hygiène publique in Paris, finding that any narcotic drug to which the present Convention does not apply is liable to similar abuse and productive of similar ill-effects as the substances to which this Chapter of the Convention applies, the Health Committee shall inform the Council of the League accordingly and recommend that the provisions of the present Convention shall be applied to such drug.

" The Council of the League shall communicate the said recommendation to the Contracting Parties. Any Contracting Party which is prepared to accept the recommendation shall notify the Secretary-General of the League, who will inform the other Contracting Parties.

" The provisions of the present Convention shall thereupon apply to the substance in question as between the Contracting Parties who have accepted the recommendation referred to above."

[8] *Records of the Second Opium Conference*, I, 284-288.

[9] The text of Article 8 reads as follows :

" In the event of the Health Committee of the League of Nations, after having submitted the question for advice and report to the Permanent Committee of the Office international d'Hygiène publique in Paris, finding that any preparation containing any of the narcotic drugs referred to in the present Chapter cannot give rise to the drug habit on account of the medicaments with which the said drugs are compounded and which in practice preclude the recovery of the said drugs, the Health Committee shall communicate this finding to the Council of the League of Nations. The Council will communicate the finding to the Contracting Parties, and thereupon the provisions of the present Convention will not be applicable to the preparation concerned."

[10] Advisory Committee, *Report to the Council*, eleventh session (April 1928), A.7.1928.XI, p. 10.

The slowness in bringing new drugs under control led Mr. Herbert May to propose in 1930 that the provisions of the 1925 Convention should be applied to all alkaloids of opium and the coca leaf and to the derivatives of all drugs mentioned in article 4 thereof, except for those found not to be addiction-producing by the Health Committee, after consultation with the Office d'Hygiène publique.[11] The Advisory Committee acknowledged the importance of making the procedure of article 10 more elastic and rapid, but could not recommend that a change be made in this procedure. Instead it proposed that the Health Committee should be asked to speed up the existing procedure and, if possible, to reduce its duration to six months.[12]

The 1931 Convention

The conference for the limitation of the manufacture of narcotic drugs met at Geneva from 27 May to 13 July 1931. Although it did not establish the system of direct limitation of manufacture which had been devised by the Advisory Committee, it adopted a plan of indirect limitation based on Parties' furnishing binding estimates of their medical and scientific needs for narcotics. The adoption of this scheme, however, made it more desirable than ever that drugs should be controlled on a uniform basis.[13] This seems to have been understood generally, for the arguments adduced at the 1924-25 conference against the application of mandatory controls to new drugs were not repeated.[14]

As regards the procedure for placing a new drug under control, most delegates to the conference were prepared to accept a German proposal whereby a new narcotic could not be manufactured unless the government found it to be of medical value and notified the Secretary-General accordingly, in order that the Health Committee make its finding as rapidly as possible. The representative of the United States of America proposed that during the " waiting period ", the system of import certificates and export authorizations should be put into operation. This approach was opposed on the ground that it would require the introduction of a world-wide control system which might have to be abandoned within two or three months. After the adoption of the German proposal, however, the United States delegation placed before the conference an amendment (the latter part of paragraph 1 of article 11 of the 1931 Convention) aimed at preventing the uncontrolled manufacture of new narcotic drugs. It provided that unless the government itself found the drug unable to produce addiction or incapable of conversion into such a drug, it must limit manufacture to quantities required for domestic medical and scientific needs and for " export orders subject to the provisions of this Convention " (thus bringing into operation the system of import certificates and export authorizations). By a vote of 18 to 10, the Conference accepted this amendment.[15]

The procedure of article 11 [16] of the 1931 Convention constituted a tremendous gain over that of article 10 of the 1925 Convention. In addition to providing for the immediate and mandatory control of such drugs on the basis of a decision by an international body and for the imposition, in most cases, of national and international controls in the meantime, this article banned the manufacture of new narcotics which were not of medical or scientific value, and created a system of notifications which kept the Parties and international organs concerned informed of the status of each new drug from the time it was manufactured for trade anywhere in the world. It also provided that the same machinery created for deciding whether new drugs should be brought under control could be used for reviewing such decisions in the light of later scientific developments and that products not themselves addiction-producing, but only convertible into such drugs, should also be controlled. However, convertible drugs of this type which are widely used in medicine might be placed under less stringent controls.[17]

The foregoing procedure was not, however, without certain shortcomings. The nature of the national controls to be applied to new drugs during the period before a decision is taken by the Health Committee is rather obscure. Article 11, paragraph 1, simply states " and the provisions of this Convention shall apply ". The Convention contains two control regimes, and the conference decided that new drugs should

[11] For the text of Mr. May's proposal, see O.C.1347 or Advisory Committee Report and Draft Convention on the Limitation of the Manufacture of Narcotic Drugs, C.168.M.62.1931.XI, Annex 2, pp. 21-22.

[12] *Ibid.*, p. 11.

[13] Otherwise, the application of the estimate system, and the limitation of manufacture to a new drug would pose certain difficulties.

[14] For the debates on this question, see *Records of the Conference for the Limitation of the Manufacture of Narcotic Drugs*, I, 168-171, 213-214, 242-244, 310 and 317.

[15] *Ibid.*, I, 168, 213-214, 242-244.

[16] The text of article 11 is as follows :

" 1. No trade in or manufacture for trade of any product obtained from any of the phenanthrene alkaloids of opium or from the ecgonine alkaloids of the coca leaf, not in use on this day's date for medical or scientific purposes shall take place in any country or territory unless and until it has been ascertained to the satisfaction of the government concerned that the product in question is of medical or scientific value.

" In this case (unless the government determines that such product it not capable of producing addiction or of conversion into a product capable of producing addiction) the quantities permitted to be manufactured, pending the decision hereinafter referred to, shall not exceed the total of the domestic requirements of the country or territory for medical and scientific needs, and the quantity required for export orders and the provisions of this Convention shall apply.

" 2. Any High Contracting Party permitting trade in or manufacture for trade of any such product to be commenced shall immediately send a notification to that effect to the Secretary-General of the League of Nations, who shall advise the other High Contracting Parties and the Health Committee of the League.

" 3. The Health Committee will thereupon, after consulting the Permanent Committee of the Office international d'Hygiène publique, decide whether the product in question is capable of producing addiction (and is in consequence assimilable to the drugs mentioned in sub-group (*a*) of group I), or whether it is convertible into such a drug (and is in consequence assimilable to the drugs mentioned in sub-group (*b*) of group I or in group II).

" 4. In the event of the Health Committee deciding that the product is not itself a drug capable of producing addiction, but is convertible into such a drug, the question whether the drug in question shall fall under sub-group (*b*) of group I or under group II shall be referred for decision to a body of three experts competent to deal with the scientific and technical aspects of the matter, of whom one member shall be selected by the Government concerned, one by the Opium Advisory Committee of the League, and the third by the two members so selected.

" 5. Any decisions arrived at in accordance with the two preceding paragraphs shall be notified to the Secretary-General of the League of Nations, who will communicate it to all the Members of the League and to the non-member States mentioned in article 27.

" 6. If the decisions are to the effect that the product in question is capable of producing addiction or is convertible into a drug capable of producing addiction, the High Contracting Parties will, upon receipt of the communication from the Secretary-General, apply to the drug the appropriate regime laid down in the present Convention according as to whether it falls under group I or under group II.

" 7. Any such decision may be revised, in accordance with the foregoing procedure, in the lights of further experience, on an application addressed by any High Contracting Party to the Secretary-Genera ."

[17] See article 11; paragraph 4, provides a special procedure for determining the control regime to be applied to substances convertible to addiction-producing drugs.

be treated temporarily as if they fell under the more drastic of these regimes.[18] The *Historical and Technical Study* on the 1931 Convention prepared by the Secretariat of the League of Nations states that manufacture should be regulated in accordance with article 6,[19] which limits it to the amounts required for domestic consumption, conversion (e.g., of morphine into codeine), export orders and stock maintenance.

A more important difficulty arose some years after the treaty came into force, as a result of the restricted scope of article 11. It may be applied only to substances " obtained from " the phenanthrene alkaloids of opium and the ecgonine alkaloids of the coca leaf and not in use on 13 July 1931. When pharmacologists began to synthesize narcotic drugs from common chemicals, it was impossible to apply to these new drugs the provisions of the 1931 Convention. Indeed a special decision of the Advisory Committee was thought necessary to interpret the treaty as applying to those derivatives of the alkaloids which were produced synthetically.[20]

Finally, there may be a question whether a procedure by which a technical decision taken by a national government is reviewed and perhaps reversed by an international organ is desirable. The Health Committee, or to-day the World Health Organization, might have the embarrassing duty of finding a drug to be addiction-producing or convertible into an addiction-producing drug after a government had found to the contrary. Furthermore, it is possible that governments might temporarily, on the basis of different experiences, reach differing conclusions regarding a new drug.

One omission from the list of drugs placed under control by the terms of the 1931 Convention itself—paracodeine (dihydrocodeine)—gave concern to the Advisory Committee. Although paracodeine is not itself addiction-producing, it is readily convertible into dihydromorphine, of which paramorfan is a salt. It was in use on 13 July 1931. Thus it could not be brought under control by article 10 of the 1925 Convention (which applies only to addiction-producing substances) or by article 11 of the 1931 Convention.

The Advisory Committee considered the omission serious enough to require legal action, and a special draft protocol to place paracodeine under the scope of the 1931 Convention was prepared.[21]

The conference for the adoption of this protocol, however, could not be convened because of the Second World War.[22]

II. The formulation of the Paris Protocol

The Nature of the Problem

Shortly before the outbreak of the Second World War, a German pharmacologist reported the discovery of pethidine, a powerful synthetic analgesic with effects similar to morphine.[23] Pethidine was the first of many such synthetic analgesics, and because—like most strong analgesics—it was addiction-producing, it created control problems of unusual complexity. After the war, these problems were explored. First of all, synthetic narcotics needed to be brought under international control, but as things stood this could be done only by means of article 10 of the 1925 Convention. A way had to be found to extend the control system of the 1931 Convention to cover them. Secondly, their provisional control, prior to a decision by the World Health Organization, presented a specially difficult problem. As yet, there was no way of delimiting these drugs in advance and it was often a time-consuming procedure for the governments of drug-manufacturing countries to determine definitely whether a new analgesic was addiction-producing or not. Thirdly, the whole concept of convertibility needed reappraisal. Modern chemistry could create narcotic drugs out of many common chemicals : was it practicable for all these to be placed under narcotics control? From this it followed that special control measures might have to be devised for these drugs, which could or might soon be manufactured illicitly with greater ease than the traditional narcotics, since it would no longer be necessary to smuggle opium or coca leaves over long distances for this purpose.

First steps towards the Paris Protocol

At its first session, in November-December 1946, the Commission on Narcotic Drugs[24] studied a memorandum of the Secretariat which proposed, *inter alia*, that a further procedure be developed for bringing new drugs under international control. The paragraph is perhaps worth quoting in full :

> " Taking into account the experience gained with regard to the international control of new drugs under articles 10 and 11 of the 1925 and 1931 Conventions respectively, the Commission may desire the Secretariat to examine the possibilities of amending the relevant provision of the 1925 and 1931 Conventions with a view to establishing a procedure for controlling new drugs which would combine the advantages of the procedure under article 10 of the 1925 Convention (wider scope of application) with those of the procedure under article 11 of the 1931 Convention (the immediate effect and binding character of the decisions of the international technical organs) ".[25]

The Commission agreed with the foregoing proposal, and the secretariat accordingly prepared a memorandum entitled " Study of Measures to be taken with a View to bringing under International Control Narcotic Drugs not covered by Conventions at present in Force ".[26]

In this memorandum, issued in July 1947, the Secretariat drew the Commission's attention to the following methods by which synthetic narcotics might be placed under mandatory full-scale international control : (1) amendment of article 10 of the 1925 Convention and of article 11 of the 1931 Convention; or (2) conclusion of a separate instrument. It was pointed out that the first method presented certain difficulties. Unless it contains provisions to the contrary, amendment of a multi-

[18] *Records of the 1931 Conference*, I, 243.

[19] P. 156.

[20] Advisory Committee, *Report to the Council*, seventeenth session (Oct.-Nov. 1933), C.642.M.305.1933.XI, p. 4.

[21] Advisory Committee, *Report to the Council*, 23rd session (June 1938), C.237.M.136.1938,XI., p. 8, and 24th session (May-June 1939), C.202. M.131.1939.XI, p. 18.

[22] Advisory Committee, *Report to the Council*, 25th session (May 1940), C.125.M.114.1940.XI., p. 6.

[23] Eisleb, O. & Schaumann, O., " Dolantin, ein neuartiges Spasmolytikum und Analgetikum (chemisches und pharmakologisches) " (Pethidine, a new spasmolytic and analgesic (chemical and pharmacological)), in *Deutsche Medizinische Wochenschrift*, 16 June 1939, 65, pp. 967-968.

[24] After the war, the Commission on Narcotic Drugs assumed the functions of the Advisory Committee, and the World Health Organization those of the Health Committee of the League of Nations and the Office international d'Hygiène publique.

[25] Memorandum of the secretariat on the terms of reference of the Commission on Narcotic Drugs, III, 5, in Annex I of the report of the Commission on Narcotic Drugs on its first session, p. 30. (Economic and Social Council, *Official Records, Second Year*, Fourth Session, Supplement No. 1).

[26] E/CN.7/80.

lateral treaty usually requires the unanimous consent of all States Parties to the original treaty. Moreover, amendment of the 1925 Convention (which contains no provisions for its amendment) to make decisions taken under article 10 immediately binding on Parties would hardly achieve the desired goal of extending to the drugs in question the control system of the 1931 Convention. Amendment of the 1931 Convention would perhaps be more straightforward, since article 33 defines the procedure to be followed. It might not, however, suffice to amend article 11, and the necessity of amending other articles where the term " drugs " was used—particularly article 1, which defines the substances under control—would have to be carefully considered.

The conclusion of a new instrument seemed the easier and quicker way of dealing with the situation. The unanimous acceptance of Parties to the 1931 Convention would not be needed, since it would contain its own provisions for entering into force as among those States who might accede to it. It might be drafted in such a way that Parties would be bound promptly to apply the control measures provided by the 1931 Convention to all drugs outside the scope of that instrument, including paracodeine.

The memorandum then set forth the following procedure by which this might be accomplished :

(1) A Party considering a narcotic drug outside the scope of the 1931 Convention to be " liable to similar abuse as the drugs specified in article 1, paragraph 2, of the 1931 Convention " notifies the Secretary-General, who notifies other Parties and the Commission on Narcotic Drugs;

(2) The Commission on Narcotic Drugs then decides (*a*) whether the notification should be submitted to the World Health Organization for examination and opinion; [27](*b*) whether the drug should be placed under temporary control pending action by the World Health Organization (the Commission's recommendation to apply as between Parties accepting it);

(3) The World Health Organization makes a finding as to the addiction liability or the possibility of conversion, and the Commission then decides whether the drug should be assimilated to the regimes established under Group I or Group II of the Convention;

(4) The Commission's decision is notified to governments, and Parties apply the proper control regime immediately upon receipt of the notification.

It was pointed out that it might be necessary to exclude opium, coca leaf, and cannabis from the scope of the Protocol,[28] and that the same procedure by which drugs were placed under control might be used as regards requests for the revision of earlier decisions.

Principles of New Protocol—Review of the Commission and the Council

At its second session (24 July - 8 August 1947), the Commission gave careful consideration to this memorandum, which was twice revised and re-issued to incorporate the Commission's decisions. [29] On the first afternoon of the session, the Commission heard, at a closed meeting, a technical report by the two experts of the United States Public Health Service on the serious addiction-producing effects inherent in amidone (methadone), one of the new synthetic analgesics. These effects were comparable to those produced by the most dangerous opiates. The experts warned that an able but unscrupulous chemist, with equipment and materials available on the open market, could secretly produce substantial quantities of this drug. They estimated that even one factory could flood the world with it and warned that many other types of synthetic narcotic might be easily developed from known formulae. The representative of the United States informed the Commission that amidone would be licensed in his country in less than two months and controlled as a dangerous drug. He cautioned, however, that this drug would soon be manufactured elsewhere and that in all probability some of it would be diverted into the illicit traffic.[30]

After learning of these developments, the Commission adopted a motion proposed by the representative of China that " it is urgent to take immediate action to bring the manufacture and distribution of amidone and other synthetic drugs under international control ".[31] The Paris Protocol was concluded within sixteen months.[32]

The Commission agreed that the best way of achieving its goal was to prepare a separate instrument.[33] As regards the procedure suggested by the secretariat, the Commission adopted it subject to the following modifications :

(1) To ensure that no addiction-producing drugs should be excluded from the Protocol, it was decided to use the term " drugs " instead of " narcotic drugs ".[34]

(2) It was decided that, in order to save time, notifications of drugs should be transmitted by the Secretary-General to the World Health Organization at the same time as they were forwarded to the Commission.[35]

(3) It was decided that the World Health Organization rather than the Commission should decide whether a drug should be assimilated to the control regime of group I or II of article I of the 1931 Convention.[36]

The Commission adopted a resolution approving a second re-draft of the above-mentioned memorandum incorporating these modifications and recommended to the Economic and Social Council that the secretariat should prepare a draft protocol for circulation to all governments concerned.[37]

---

[27] The Commission had been designated in this connexion for the following reason : the memorandum had attempted to adhere to the procedure adopted by the 1931 Conference, except to simplify it where possible. The records of the conference showed that it had been intended to give a body of the League of Nations the first opportunity of examining a question of this nature. Furthermore, the decisions to be taken were of a dual nature—medical and scientific, on the one hand, and administrative and technical, on the other. Under the new organizational arrangement, among the possible organs these latter functions would have naturally devolved upon the Commission. (E/CN.7/106, pp. 43-44.)

[28] The provisions of the 1931 Convention, and therefore of the Protocol, were not particularly suitable for application in their present form to these substances, and special control procedures for them have been included in other instruments.

[29] As E/CN.7/80/Rev.1 and E/CN.7/80/Rev.2.

[30] See report of the Commission on Narcotic Drugs on its Second Session, E/575, pp. 13-15.

[31] Commission on Narcotic Drugs, Second Session, *Summary Record of the Second Meeting*, E/CN.7/106, p. 12.

[32] The two dates were 24 July 1947 and 19 November 1948.

[33] E/575, p. 15.

[34] E/CN.7/106, pp. 16-17.

[35] E/CN.7/106, pp. 42-45, 89-90.

[36] E/CN.7/106, pp. 17-20. This decision constituted a departure from the procedure of article 11, paragraph 4, of the 1931 Convention, which had provided for the government concerned and the Advisory Committee to set up a small committee for the purpose. (In this connexion, see the explanation given in E/CN.7/106, pp. 90-91.)

[37] E/CN.7/106, p. 93; E/575, p. 15.

The Commission also recommended that the draft protocol be transmitted to the Interim Commission of the World Health Organization for its comments.[38]

On 13 August 1947, the Council, which as it happened was meeting simultaneously with the Commission, adopted a resolution carrying out this recommendation of the Commission. In acting immediately, without requiring the usual six weeks' notice for inclusion of an item on its agenda, the Council granted a request for urgent action conveyed in a letter of the Chairman of the Commission.[39]

The Secretary-General prepared the draft protocol, and in December 1947 and January 1948 copies were forwarded to the governments concerned for their comments.[40]

Meanwhile, during the second session of the General Assembly, at meetings of the Third Committee, several representatives expressed support for the Protocol and called attention to the urgent need for its conclusion.[41]

By the time the Commission reconvened for its third session (3-22 May 1948), twenty-six replies had been received, of which only seven contained observations on the draft Protocol.[42] Two Governments—those of the United Kingdom and the United States—suggested important changes in the procedure which the Commission had recommended at its previous session. Both changes related to the central problem faced by the framers of the Protocol—to find a way of placing new addiction-producing drugs under control rapidly, yet without delaying unduly the manufacture and distribution of new therapeutic agents.[43] The United States proposed the temporary limitation by all parties of the manufacture and distribution of a new drug suspected of being addiction-producing to quantities needed for purposes of research from the time when it was notified by a Party until the World Health Organization had made its finding. The United Kingdom, on the other hand, considered that it would be preferable, in order to expedite matters, for the Commission on Narcotics Drugs to take the necessary decision regarding the placing of new drugs under international control.

The United States proposal was supported by the following arguments : the fact that a State had notified a new drug would amount to *prima facie* evidence that it was at least potentially dangerous, and the temporary waiting period would enable Parties to perfect and put into operation control plans, especially to limit manufacture and distribution to medical and scientific needs, *before* large quantities of the drug had been manufactured. However, this scheme clearly entailed some delays in making new drugs available to the medical profession, and would run counter to existing laws in several countries. It was also implied that the procedure might be exploited for commercial advantage, since if a new drug—perhaps even one which was obviously not addiction-producing—were notified, its manufacture for trade might be delayed for a period of months.[44]

The United Kingdom considered that the Commission could act more rapidly than the World Health Organization, especially if a decision of the relevant body of experts required confirmation by the Executive Board and the World Health Assembly. The representative of the World Health Organization, however, assured the Commission that findings could be made promptly, and many members were reluctant to take responsibility for what amounted to a technical decision.

The Commission therefore decided not to change this provision, but in order to go part of the way towards solving the difficulty which had given rise to these proposals, it strengthened the complementary provision for placing new drugs under provisional control pending action by the World Health Organization. It decided that the Commission's power to place new drugs under provisional control should be mandatory rather than recommendatory.[45]

That available information regarding a new drug should be submitted both by the Party notifying it and by Parties receiving notifications was proposed respectively by the Philippines and the United Kingdom. The Commission decided that a provision regarding the notifying Party should be included in the Protocol itself, while as regards other Parties, a clause in the Final Act or in a resolution by the General Assembly would suffice.[46]

Colombia proposed that the Protocol should require the periodic publication of a list of addiction-producing drugs, preparations and patent medicines, but the Commission decided it that was unnecessary to refer to this task in the Treaty.[47]

Various changes in the final clauses were also suggested and accepted by the Commission, particularly for the procedures for adherence and entry into force, denunciation and application to territories.[48]

The Commission incorporated its decisions in a revised draft of the Protocol which, with very minor drafting changes (except for the clauses regarding territorial application and denunciation), was adopted without further modification.[49] It concluded its work on the draft instrument by proposing to the Economic and Social Council the adoption of a resolution which would : (i) request the Secretary-General to forward the new draft, as approved by the Council, to governments for their comments; (ii) recommend that the General Assembly approve the Protocol after taking into account any new observations received from governments and fix the earliest possible date during the third session when the Protocol might be opened for signature; and (iii) recommend to Members that their delegates to the forthcoming Assembly should be given the necessary full powers to adhere to the Protocol.[50]

In June 1948, the secretariat sent copies of the revised text of the draft Protocol to governments and requested them to submit their observations in time for the seventh session of

[38] E/529, p. 4.

[39] See document E/529 for the text of this letter, the special report of the Commission on this subject and the text of the Commission's resolution. The short debate of the Council appears in the Official Records of the fifth session, pp. 230-231.

[40] By circular note CN.33.1947.NARCOTICS.

[41] See A/C.3/SR.54, 55 and 62 for these comments.

[42] The texts of these observations were reproduced, in part, in E/798, pp. 7-18, and in E/CN.7/115, Adds. 1-2.

[43] This problem is not made any easier by the fact that usually the therapeutic effects of a drug are more readily, and therefore more rapidly, determined than the addiction-producing effects or the conversion liability.

[44] E/798 contains the Commission's decisions; E/CN.7/155, pp. 18-23, 30-55 contains the summary records of the Commission's debates on this question.

[45] E/798, pp. 10, 12-13.

[46] E/798, p. 10.

[47] E/CN.7/155, p. 23.

[48] E/798, pp. 13-19.

[49] The final text of the substantive articles (1-4) of the Paris Protocol has been reproduced at the end of the present article.

[50] E/798, pp. 1-2.

the Economic and Social Council, which was to begin on 19 July 1948.[51] No observations were, however, received early enough for submission to the Council.[52]

The special report of the Commission on the draft Protocol[53] including the revised text of the Protocol and the draft resolution, were examined on 22-23 July 1948 by the Social Committee[54] of the Economic and Social Council and on 3 August by the plenary Council.[55] Apart from one minor drafting change, the substantive clauses were approved without modification. A debate developed, however, over the territorial clause, during which some delegations proposed that it should be deleted, while others considered that this would greatly delay ratification by metropolitan countries. A new clause, also acceptable to the metropolitan powers, was eventually adopted by the Committee, and the Council rejected a proposal to delete it by a vote of 11 to 3, with 4 abstentions.[56]

The Council, by a vote of 15 to 2, with 1 abstention, adopted the draft resolution proposed by the Commission after including in it two further recommendations to the General Assembly : (i) to urge all states to adhere to the Protocol as soon as possible; and (ii) to urge states to take as soon as might be the necessary steps to extend the application of the Protocol to territories for whose foreign relations they were responsible—subject, where necessary for constitutional reasons, to the consent of the governments of those territories.[57]

On 25 August 1948, a third circular note on the Protocol was addressed to governments, communicating a third draft of that instrument embodying the changes made by the Council.

Not many more comments of a substantial character were received from governments. Sweden urged that the decisions the Commission on Narcotic Drugs placing new drugs under temporary international control should be limited to recommendations to governments. The Netherlands also favoured this idea, but agreed that the acceptance of preliminary decisions by the Commission would, in general, create no difficulties. Several other countries stated that they had no observations to submit.[58]

When the General Assembly convened in September 1948, the Third Committee gave priority to consideration of the draft Protocol, discussing it at three meetings on 29 and 30 September 1948.[59]

The discussion revolved mostly around the territorial clause. A proposal, which, in effect, would have reversed the Council's decision on this point, was rejected on a roll-call vote by 25 to 17, with 11 abstentions.[60] The territorial clause was then adopted by a vote of 33 to 8, with 12 abstentions, and the Committee concluded its examination of the draft instrument by unanimously adopting it.[61]

The Committee then turned to the draft resolutions which the General Assembly would adopt at the same time as the Protocol. After a short discussion, it agreed on a draft resolution whereby the General Assembly would : (i) register its approval of the Protocol; (ii) urge Member States and invite non-member States to sign or accept it as soon as possible; (iii) urge Member States not signing or accepting it to communicate their reasons to the Secretary-General, and (iv) urge States having territories for which they bore international responsibilities to take the necessary measures to extend the application of the Protocol to such territories and to send the Secretary-General a list of those territories to which the Protocol had not been applied as of 31 August 1949, together with the reasons why the necessary declaration had not been made.[62]

The penultimate step in the long chain of events by which the Paris Protocol was enacted took place on 8 October 1948, when the draft instrument was brought before the 150th plenary session of the General Assembly. Although the question of the territorial clause was again raised, the occasion was rather one for summation than detailed consideration.

During the course of the proceedings, the representative of the Lebanon drew attention to the extraordinary speed with which the Protocol had been brought into being, and emphasized that this had been possible only through the utilization of the machinery of the United Nations. The representative of the USSR called the Protocol " a certain step forward in the . . . struggle waged to-day against the widespread use of narcotics ". The representative of the United States expressed gratification that the Protocol was acceptable to all representatives, for otherwise there might be gaps in the network of narcotics control. Again, the representative of China termed the Protocol a " turning-point in the campaign against the ever present danger of the abuse of narcotic drugs and of drug addiction.[63]

The Protocol and its accompanying resolutions were then unanimously approved by the highest body of the United Nations.

The Secretary-General arranged that the ceremony at which the plenipotentiaries of Governments would affix their signatures to the Protocol should take place at the Palais de Chaillot on 19 November 1948. At 4 p.m. on that day, forty-seven plenipotentiaries from forty-six countries convened to affix their signatures to the Protocol. Mr. H. Laugier, Assistant Secretary-General in charge of the Department of Social Affairs, welcomed the plenipotentiaries on behalf of the Secretary-General and reviewed briefly the events. He concluded with the following statement :

" To-day marks the end of the first phase of the effort by the United Nations, working as an organization, to bring synthetic drugs under international control. The next step must lie with individual Governments and it is now for them so to act that the Protocol may come into force at the earliest possible date. But in addition to this, one final but vitally important factor remains : it is that the successful control of illicit traffic in narcotic drugs is above

[51] C.N.62.1948 NARCOTICS, dated 9 June 1948.

[52] See, in this connexion, E/AC.7/SR.43, p. 6. The Council was meeting in Geneva, and replies began to reach New York during the month of July. They were published in E/1056, issued in September 1948.

[53] E/798.

[54] See E/AC.7/SR.43-45; also report of the Social Committee to the Council, E/902.

[55] E/SR.189.

[56] E/902, pp. 1-3, summarizes the debate in the Social Committee; and E/SR.189, pp. 4-14, contains a record of the Council's discussion.

[57] E/SR.189, p. 14; the resolution was numbered 159 I (VII) in the Council series.

[58] E/1056; United Nations registry file SOA 323/2/01 contains some unpublished replies.

[59] 86th to 88th meetings, see A/C.3/SR.86-88 for the summary records of these meetings.

[60] A/C.3/SR.87, p. 5.

[61] *Ibid*, p. 6.

[62] The text appears in A/666, p. 2.

[63] A/SR.150, 1-26.

all else dependent upon international co-operation. This fact was emphasized by every representative who took part in the debate in the General Assembly, where it was stated again and again that the provisions of the Protocol must be universally applied if the dangers from these drugs to which I have already referred are to be averted. I therefore trust that all States will scrupulously apply the provisions of the Protocol at all times, in the spirit as well as the letter of the General Assembly's resolution of 8 October ".

Twelve plenipotentiaries signed the Protocol without reservation to acceptance; the others signed subject to confirmation by national legislatures. Australia, New Zealand, the United Kingdom and the United States made declarations applying the provisions of the Protocol to certain territories for whose foreign relations they bore the responsibility. At the close of the ceremony, Mr. Laugier affixed the seal of the United Nations to the Protocol.[64]

The Paris Protocol was, in a very real sense, the necessary complement of article 11 of the 1931 Convention. It made it possible to place all manufactured narcotic drugs under mandatory world-wide control, which had considerable effect even in countries where the Protocol itself was not in force.

The Protocol, however, left two problems partly solved or unsolved. It did not go so far as the 1931 Convention, which required governments, as soon as they began to manufacture for trade certain categories of drug, to place them under national control. The period between the commencement of manufacture and action by the Commission or the World Health Organization, as the case might be, left the door open, legally speaking, for abuses. This period might last a year or so, but in view of the fact that the Commission and the World Health Organization Expert Committee on Drugs Liable to Produce Addiction generally meet in spring and autumn respectively, the period need not be longer than six months, provided that the addiction-producing effects of a new analgesic are studied promptly. If a new analgesic were developed and placed in use by a country which did not possess facilities for testing its addiction-producing effects, the World Health Organization might have difficulty in reaching a rapid decision, and the Commission's role would be crucial.

In point of fact, this situation has not been exploited by traffickers, probably because governments and most drug manufacturers are aware of the problem and have a genuine desire to protect public health. However, if a way can be found to delimit in advance the substances which are liable to produce addiction—for example, by their chemical formulae or by reference to the possible relationship between strongly analgesic properties and addictive qualities—or if a very serious control problem were to develop, a plan to place any drug notified under temporary control would probably be adopted. Such a plan would complete the circle of legal world-wide controls on all addiction-producing drugs.[65]

The framers of the Protocol did not attempt to clarify the concept of convertibility. The need for such clarification has been brought about by new developments in chemistry and pharmacology that have made it increasingly unrealistic to attempt to control in the traditional way all substances convertible into addiction-producing drugs. But the Protocol, which was designed to complement the provisions of the 1931 Convention could hardly deal with this question without complicating the situation as regards the other instrument. There are many factors to be weighed—the ease with which convertibility can be effected, the usefulness of the substance for, say, industrial purposes, and the feasibility of controlling it from the administrative or technical standpoints. In this connexion, too, the possibility of further scientific advances has to be borne in mind. Probably as much flexibility as possible is needed to allow a decision to be taken on the basis of the special circumstances surrounding each case.

The World Health Organization has already attempted to clarify the meaning of the term " convertible " as used in the narcotic treaties. On 17 May 1954, the seventh World Health Assembly adopted an interpretation whereby a substance would be considered as convertible " where the ease of conversion and the yield obtained constitute a risk to public health, and that in cases where there is uncertainty as to whether a substance will fall under this definition, the substance will be considered as ' convertible ' rather than as ' not convertible ' ".[66]

III. The Paris Protocol, 1948–1956

Ratification and Implementation

Despite the unanimous approval of the General Assembly and the special resolution calling for speedy and universal adherence, the Paris Protocol has hitherto had only a moderately successful record in terms of numbers of actual ratifications. The Protocol came into force on 1 December 1949, and there were, on 1 March 1956, forty-seven States Parties,[67] as compared with fifty-six States Parties to the 1946 Protocol and approximately seventy States Parties to the 1931 Convention. Of the eleven principal drug-manufacturing countries listed in article 6, however, all have become Parties to the instrument. Furthermore, judged on the basis of popular coverage, the great majority of the world's inhabitants live in countries or territories where the Protocol is in force.[68]

The international bodies interested in narcotics control have done all they could to increase the number of Parties. In 1952 and 1954, the Economic and Social Council, on the proposal of the Commission, adopted resolutions calling for governments which had not already done so to adhere to the Protocol.[69] In 1955, the Council asked the Secretary-General to invite the governments concerned to report on the steps taken in pursuance of its resolution of the previous year.[70] The Permanent Central Opium Board and the Drug

[64] See E/CN.7/152 for the Summary Record of the ceremony.

[65] It may be noted that the Commission on Narcotic Drugs is already considering this possibility favourably for inclusion in the draft Single Convention. The possibility of circumscribing substances liable to produce addiction by chemical formulae is being studied by the World Health Organization and the Secretariat.

[66] Seventh World Health Assembly, WHA7.7, 17 May 1954.

[67] These include the following States : Afghanistan, Albania, Australia, Austria, Belgium, Burma, Byelorussian SSR, Canada, Ceylon, China, Czechoslovakia, Denmark, Egypt, Ethiopia, Finland, France, Greece, India, Indonesia, Iraq, Ireland, Israel, Italy, Japan, Laos, Lebanon, Luxembourg, Mexico, Monaco, Netherlands, New Zealand, Norway, Pakistan, Philippines, Poland, Saudi Arabia, Spain, Sweden, Switzerland, Turkey, Union of South Africa, Union of Soviet Socialist Republics, United Kingdom, United States of America, Viet Nam, Yemen and Yugoslavia.

[68] Declarations made under article 8 of the Protocol have extended its application to most of the non-self-governing territories of adhering metropolitan countries. In terms of population, the largest gaps are in east central Europe and South America.

[69] Resolutions 436 G (XIV) and 548 H I (XVIII).

[70] Resolution 588 D I (XX).

Supervisory Body have also, on several occasions, emphasized the importance of States becoming Parties to the Paris Protocol.[71] However, a number of countries which signed the Protocol have still to ratify it.[72]

In 1953, the Secretariat tried to set out the extent to which governments had assimilated the new synthetic drugs to their national control systems for narcotic drugs by surveying the national legislations. The results were published under the title *A Survey of the Synthetic Narcotic Drugs, their Salts and Preparations placed under national control in the various countries and territories.*[73] It was found, for example, that pethidine was controlled in at least forty-eight countries, in fifteen of which the Protocol was not in force at the time. The corresponding figures for methadone were forty and ten. For the other drugs, the figures were somewhat lower. In view of the incompleteness of the information at the secretariat's disposal, it is likely that decisions taken under the Protocol are widely and rather rapidly translated into terms of national legislation, and it would appear that many countries which have not acceded to the Protocol nevertheless co-operate in applying its provisions within their territories.[74]

Another survey of this situation was carried out recently by the secretariat of the Permanent Central Opium Board. It was found that all but three of the forty-one States that have not yet become Parties to the Paris Protocol have submitted estimates of their needs for synthetic drugs to the Drug Supervisory Body. The situation is about the same as regards the relevant statistics on trade, manufacture and consumption furnished to the Board. It is also known that about two-thirds of these States have placed one or more synthetic drugs under national narcotics controls.[75]

More than thirty drugs have been placed under control by virtue of the Paris Protocol—a larger number than are controlled under all other instruments combined.[76] On 9 and 12 January 1950, the first group of twelve drugs was notified to the Secretary-General by the Government of the United States, and on 5 March 1951, the date on which the Secretary-General for the first time communicated to governments a notification under article 1, paragraph 4, of the Protocol, or shortly thereafter, the World Health Organization's decision to place these substances under international control began to become effective for Parties.[77] A second notification was communicated to governments on 15 May 1952, and thereafter on an average of once a year.[78] At its sixth session, the Commission invoked the provisions of article 2 of the Protocol by placing two new drugs under provisional control,[79] but the Expert Committee on Drugs Liable to Produce Addiction of the World Health Organization has carried out its functions so expeditiously that no occasion has arisen to repeat this procedure.

The foregoing account of how the Paris Protocol came into being has shown that that instrument was concluded when the time was ripe for this step forward. It has had considerable success in forestalling any large-scale abuse of the array of new addiction-producing analgesics that have come into medical use during the past ten years. However, it would be dangerous to assume that there is no longer need for concern. As has been pointed out on several occasions in the Commission,[80] the Protocol is not a final solution of this new problem. It will doubtless be necessary to keep abreast of the difficulties which the widespread use of synthetic narcotics for medical purposes have created.

---

[71] For the Drug Supervisory Body, see the 1954 and 1955 statements (E/DSB/12, p. 11; E/DSB/13, p. 6), and for the Permanent Central Opium Board, the 1954 and 1955 reports (E/OB/10, p. 17, and E/OB/11, p. 16).

[72] The following are the twenty-two signatories which have not yet ratified : Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Liberia, Liechtenstein, Nicaragua, Panama, Paraguay, Peru, Romania, San Marino, Ukrainian Soviet Socialist Republic, Uruguay and Venezuela.

[73] E/CN.7/260.

[74] E/CN.7/260, pp. 5-9, 21-25.

[75] E/OB-DSB/W.66, pp. 3-4.

[76] These include about thirty synthetic drugs which are listed in the present issue of the *Bulletin* in the article " Development of Synthetic Narcotic Drugs ". In addition to these, two derivatives of opium alkaloids have been brought under international control by virtue of article 1 of the Paris Protocol :

Drug	*Control regime*
(1) Acetyldihydrocodeine and its salts	Group II
(2) Dihydrocodeine and its salts	Group II

Drugs controlled under the 1931 Convention are placed either in Group I, a strict control regime for drugs such as morphine, or in Group II, a milder control regime for drugs such as codeine, which are widely used and merely convertible into addiction-producing drugs.

Futhermore, the following derivatives of opium alkaloids have been brought under international control since 1946 by virtue of article 11 of the 1931 Convention :

Drug	*Control regime*
(1) Methyldihydromorphinone (metopon) and its salts	Group I
(2) 6-methyldihydromorphine and its salts . . .	Group I
(3) β-4 morpholinylethylmorphine and its salts.	Group II
(4) 6-methyl- Δ^6-desoxymorphine and its salts .	Group I
(5) Dihydrohydroxymorphinone and its salts . .	Group I

Finally, the myristyl ester of benzylmorphine and its salts have been found to be convertible into an addiction-producing drug by the World Health Organization and the question of the control regime to be applied to these has not yet been determined by the body of three experts provided for in article 11, paragraph 4, of the 1931 Convention. In the meantime, the drug is being controlled as if it fell under group I.

[77] Control applies in respect of each Party only from the moment of receipt of the Secretary-General's notification.

[78] E/CN.7/260, p. 2.

[79] E/1998,paragraphs 62-66.

[80] For the most recent occasion, see the following statement contained in the report of the Commission on its tenth session :

" While the Commission considers that this protocol constitutes a very valuable interim measure, it believes that in preparing the provisions of the new convention, it must pay particular attention to certain special aspects of synthetic narcotics which have created new dangers or at least have accentuated existing ones. As far as narcotics control is concerned, synthetic narcotics differ from natural ones mainly in the following respects :

" (*a*) Although it is generally considered feasible to place under a rigid control regime the plants from which the raw materials of natural narcotics are obtained as well as these materials themselves, it seems hardly possible to subject the chemicals from which the synthetic narcotics are made and which are widely used outside the drug industry, to the traditional measures of narcotics control;

" (*b*) Although the number of natural narcotics is not very large, there could theoretically be an unlimited number of synthetic narcotics;

" (*c*) Although it has been possible to define in advance the naturally occurring chemical groups which are potentially addiction-producing, i.e., the products obtained from the phenanthrene alkaloids of opium and ecgonine alkaloids of the coca leaf, and to subject them to provisional control, it has not yet been found possible to apply a similar procedure to synthetics." (E/2768, paragraph 91.)

TEXT OF THE PREAMBLE AND ARTICLES 1-4 OF THE PARIS PROTOCOL

Preamble

The States Parties to the present Protocol,

Considering that the progress of modern pharmacology and chemistry has resulted in the discovery of drugs, particularly synthetic drugs, capable of producing addiction, but not covered by the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, as amended by the Protocol signed at Lake Success on 11 December 1946,

Desiring to supplement the provisions of that Convention and to place these drugs, including their preparations and compounds containing these drugs, under control in order to limit by international agreement their manufacture to the world's legitimate requirements for medical and scientific purposes and to regulate their distribution,

Realizing the importance of the universal application of this international agreement and of its earliest possible entry into force,

HAVE RESOLVED to conclude a Protocol for that purpose and have agreed upon the following provisions :

CHAPTER I
CONTROL

Article 1

1. Any State Party to the present Protocol which considers that a drug which is or may be used for medical or scientific purposes and to which the Convention of 13 July 1931 does not apply, is liable to the same kind of abuse and productive of the same kind of harmful effects as the drugs specified in article 1, paragraph 2, of the said convention, shall send a notification to that effect, with all material information in its possession, to the Secretary-General of the United Nations, who shall transmit it immediately to the other States Parties to the present Protocol, to the Commission on Narcotic Drugs of the Economic and Social Council and to the World Health Organization.

2. If the World Health Organization finds that the drug in question is capable of producing addiction or of conversion into a product capable of producing addiction, this organization shall decide whether the drug shall fall :

(*a*) Under the regime laid down in the 1931 Convention for the drugs specified in article 1, paragraph 2, group I, of that convention; or

(*b*) Under the regime laid down in the 1931 Convention for the drugs specified in article 1, paragraph 2, group II, of that convention.

3. Any decision or finding in accordance with the preceding paragraph shall be notified without delay to the Secretary-General of the United Nations, who shall transmit it immediately to all States Members of the United Nations, to non-member States Parties to this Protocol, to the Commission on Narcotic Drugs and the Permanent Central Board.

4. Upon receipt of the communications from the Secretary-General of the United Nations notifying a decision under paragraph 2 (*a*) or (*b*) above, the States Parties to this protocol shall apply to the drug in question the appropriate regime laid down by the 1931 Convention.

Article 2

The Commission on Narcotic Drugs, upon receipt of the notification from the Secretary-General of the United Nations in accordance with paragraph 1 of article 1 of this protocol, shall consider as soon as possible whether the measures applicable to drugs specified in article 1, paragraph 2, group I, of the 1931 Convention should provisionally apply to the drug in question, pending receipt of the decision or finding of the World Health Organization. If the Commission on Narcotic Drugs decides that such measures should provisionally apply, this decision shall be communicated without delay by the Secretary-General of the United Nations to the States Parties to this protocol, the World Health Organization and the Permanent Central Board. The said measures shall thereupon be applied provisionally to the drug in question.

Article 3

Any decision or finding taken under article 1 or article 2 of this Protocol may be revised in the light of further experience, in accordance with the procedure provided in this chapter.

CHAPTER II
GENERAL PROVISIONS

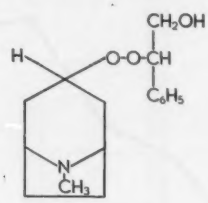
Article 4

The present Protocol does not apply to raw opium, medicinal opium, coca leaf or Indian hemp as defined in article 1 of the International Convention relating to Dangerous Drugs signed at Geneva on 19 February 1925, or to prepared opium as defined in chapter II of the International Opium Convention signed at The Hague on 23 January 1912.

Development of Synthetic Narcotic Drugs

The history of synthetic drugs with morphine-like effect is relatively short, dating back only to 1939, when Eisleb (1, 2) produced the now famous 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester (pethidine, dolantin, demerol, dolosal. etc.). Research had, however, been carried out previously for a number of years in an effort to produce synthetic substances similar to morphine in structure. This work was to a large extent undertaken by Small, Eddy and their co-workers (3) at the United States Public Health Service. The experiments were carried out under the presumption that the analgesic effect of morphine was inherent in the phenanthrene, dibenzofuran and carbazole nucleus, these products being found to be break-down products of morphine. The earlier efforts, however, did not lead to any synthetic compound with an appreciable analgesic effect.

As is often the case in organic chemistry, the results obtained were not exactly those looked for. Eisleb & Schaumann were searching for a compound which could be a substitute for atropine (4). As will be seen from the following formula, atropine contains a piperidine nucleus :



In testing the compounds which Eisleb produced (4), it was found that some of them, besides their spasmolytic properties, had also pronounced analgesic qualities. The compound which showed the best results was the carboxylic acid ester, which was subsequently marketed in Germany under the name of dolantin, and which was first thought to be non-addiction producing and therefore advertised as such. This assumption was later found to be wrong.

On the basis of this most interesting finding, research was intensified, and a great many compounds were discovered possessing morphine-like effect (5). One of the most important was methadone and its derivatives, which although originally discarded by German scientists as being too toxic, was later found, when tested in America, to possess, used dose by dose, the same analgesic effect as morphine itself (6).

There are today a large number of compounds which have been synthesized and shown to have morphine-like activity. Up to the present about thirty have been put under international control. These compounds may be classified in five major groups, according to their different basic chemical structure.

Pethidine group :

Pethidine (1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester) (7);
Bemidone (1-methyl-4-(3-hydroxyphenyl)-piperidine-4-carboxylic acid ethyl ester, 1-methyl-4-metahydroxyphenyl-piperidine-4-carboxylic acid ethyl ester) (7);
Ketobemidone (4-(3-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone, 1-methyl-4-metahydroxyphenyl-4-propionyl-piperidine) (7);
Alphaprodine (α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine) (7);
Betaprodine (β -1,3-dimethyl-4-phenyl-4-propionoxypiperidine) (7);
Betameprodine (β -1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine) (9);
1-[2-(p-aminothenyl-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester (1-[2-(p-aminophenyl)-ethyl]-4-carbethoxy-4-phenylpiperidine) (12);
1-(2-hydroxy-2-phenyl-ethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester (4-carbethoxy-1-(2-hydroxy-2-phenyl-ethyl)-4-phenylpiperidine) (12);
1-methyl-4-phenylpiperidine-4-carboxylic acid isopropyl ester and other esters of 1-methyl-4-phenylpiperidine-4-carboxylic acid (11).

Methadone Group :

Methadone (4,4-diphenyl-6-dimethylaminoheptanone-3,6-dimethylamino-4,4-diphenyl-3-heptanone) (7);
Isomethadone (4,4-diphenyl-5-methyl-dimethylaminohexanone-3, 6-dimethylamino-5-methyl-4,4-diphenyl-3-hexanone) (7);
Alpha-methadol (α-4,4-diphenyl-6-dimethylaminoheptanol-3,α-6-dimethylamino-4,4-diphenyl-3-heptanol) (7, 9, 10);
Beta-methadol (β-4,4-diphenyl-6-dimethylamino-3-heptanol,β-6-dimethylamino-4,4-diphenyl-3-heptanol) (7, 11);
Alpha-acetylmethadol (α-4,4-diphenyl-6-dimethylamino-3-acetoxyheptane, α-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane) (7, 8, 10);
Beta-acetylmethadol (β-4,4-diphenyl-6-dimethylamino-3-acetoxyheptane, β-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane) (7, 8, 10);
Phenadoxone (4,4-diphenyl-6-morpholinoheptanone-3, 6-morpholino-4,4-diphenyl-3-heptanone) (7);
4,4-Diphenyl-6-dimethylamino-3-hexanone (11);
4-Morpholino-2,2-diphenyl ethyl butyrate (ethyl-2,2-diphenyl-4-morpholinobutyrate) (12);
4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane (12);
4,4-Diphenyl-6-piperidino-3-heptanone (6-piperidino-4,4-diphenylheptan-3-one) (11).

Morphinan group :

Levorphan ((-)-3-hydroxy-N-methylmorphinan) (10);
Racemorphan ((±)-3-hydroxy-N-methylmorphinan) (7, 9, 10);
Levomethorphan ((-)-3-methoxy-N-methylmorphinan) (9, 10);
Racemethorphan ((±)-3-methoxy-N-methylmorphinan)(9);
3-Hydroxy-N-phenethylmorphinan (12).

Dithienylbutenylamine group :

Dimethylthiambutene (3-dimethylamino-1,1-di-(2'-thienyl) -1-butene) (10);
Ethylmethylthiambutene (3-ethylmethylamino-1,1-di-(2'-thienyl)-1-butene) (10);

Diethylthiambutene (3-diethylamino-1,1-di-)2'-thienyl(-1-butene) (10, 12).

Hexamethylenimine Group :

1,3-Dimethyl-4-phenyl-4-propionoxyhexamethyleneimine (12).

Few of these compounds are at present used clinically to any great extent, the majority being still in the stage of pharmacological or clinical trial. The following are at present used in medicine :

Synthetic analgesics

Pethidine

Pethidine is by far the most widely used synthetic drug with morphine-like effect. Besides its analgesic properties it also has spasmolytic action, which gives it a certain advantage over morphine in cases where pain is caused by spasms.

The world manufacture of pethidine, according to the reports of the Permanent Central Opium Board (13), is as follows :

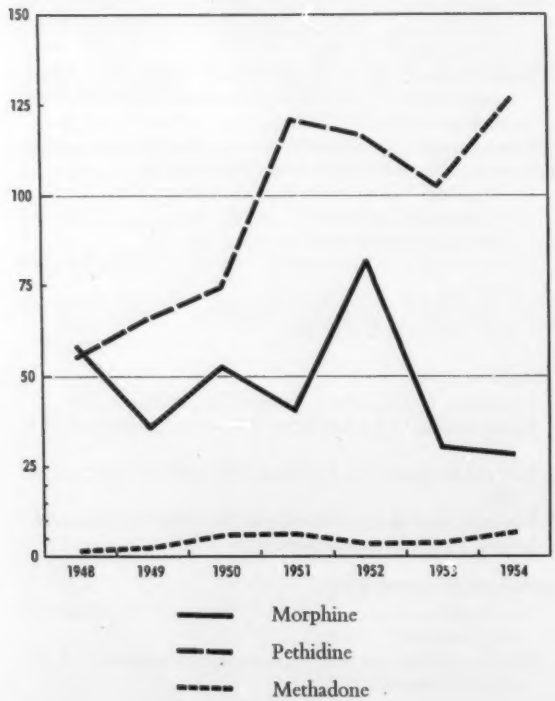
	Kg.
1950	7,423
1951	12,154
1952	11,612
1953	10,320
1954	12,555

(See also diagram 1)

Diagram 1

Manufacture of morphine, pethidine and methadone in the world

(In hundred kg)



In some countries, the consumption of pethidine has greatly increased, as may be seen from the figures given below, by way of example, on the consumption of pethidine per million inhabitants in the United States of America, the United Kingdom and France (13).

	U.S.A.	*U.K.*	*France*
	(Kg per million inhabitants)		
1950	34.55	15.21	8.18
1951	36.68	17.54	4.88
1952	42.23	18.61	3.92
1953	41.81	19.34	4.85
1954	44.15	23.43	5.46

(See also diagram 2 where pethidine and morphine consumption are compared.)

Diagram 2

Consumption of morphine and pethidine in the United States of America

(in kg per million inhabitants)

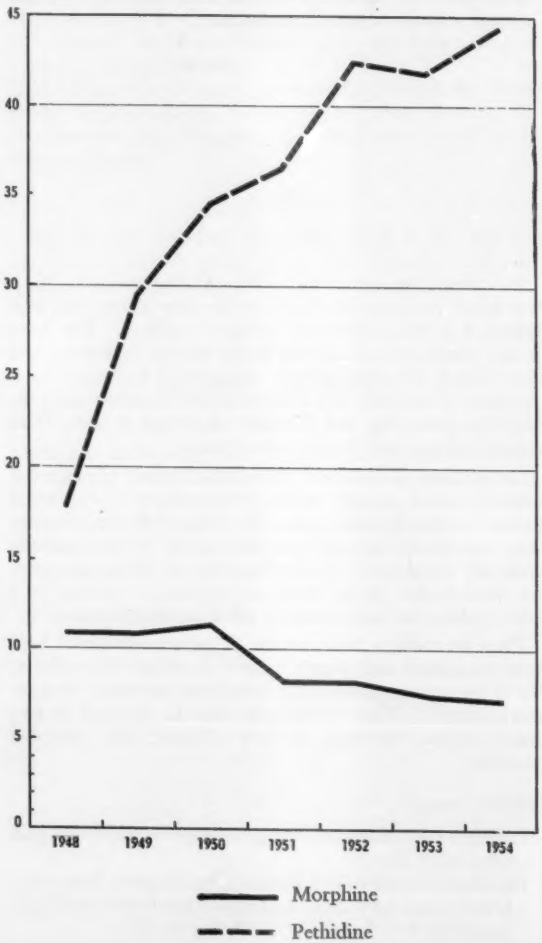
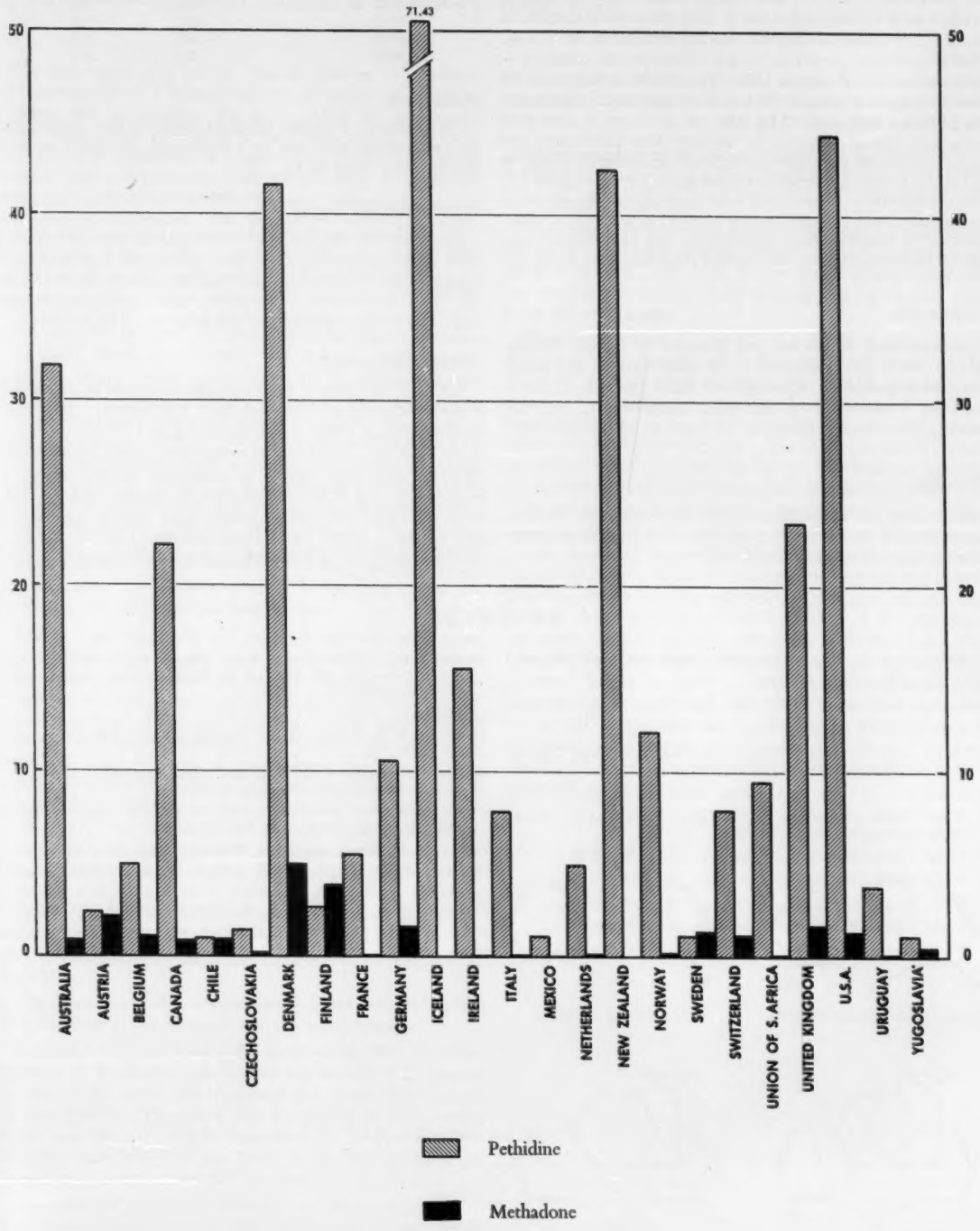


Diagram 3

CONSUMPTION OF PETHIDINE AND METHADONE IN 1954
(in kg per million inhabitants)



Ketobemidone

Ketobemidone was first produced by Eisleb (14). It has been reported to have an analgesic activity as strong as that of morphine (15). The first clinical experiments on former addicts gave the impression that it was a particularly dangerous drug (7), therefore production was not initiated in the U.S.A. Ketobemidone is, however, being produced in two countries—Switzerland and Denmark (13). The world consumption of this drug totalled 64 kg in 1954, and the estimated requirement for 1956 is a little over 72 kg (16).

The Economic and Social Council, at its eighteenth session (1954) (17), took a resolution urging governments to prohibit the manufacture, import and export of this drug, its salts, preparations and preparations of its salts; as a result, a great number of countries have discontinued the manufacture and use of Ketobemidone or have stated their intention to do so.

Alphaprodine

Alphaprodine, which was first prepared by Berger, Ziering & Lee (1947) (18) is reported to be from three to five times as active as pethidine. Owing to its short analgesic action it has been found useful in obstetrical analgesia (19), and the world production was 24 kg. in 1953 and 52 kg. in 1954 (13).

Methadone

Methadone has approximately the same analgesic effect as morphine (20) and, next to pethidine, is the synthetic drug most extensively used in the world.

The annual manufacture and consumption was the following (13) :

	Manufacture (Kg)	*Consumption* (Kg)
1951	521	388
1952	381	395
1953	395	489
1954	609	553

Phenadoxone

Phenadoxone, a slightly stronger analgesic than methadone (21), is manufactured only on a small scale, the world production in 1954 being 38 kg. (13).

Racemorphan and Levorphan

Racemorphan and levorphan are compounds which chemically closely resemble morphine. The active principle of racemorphan is levorphan. Levorphan is more than twice as efficient as an analgesic as morphine, and its effect lasts longer (22). The world production of this drug was 12 kg in 1954 (13).

Synthetic Antitussives

About 90 per cent of the morphine produced in the world is converted into codeine and other antitussives. The total consumption of codeine was 68,473 kg in 1954 (13). As far as the synthetic antitussives are concerned, only 6-dimethylamino-4,4-diphenylhexanone, a component of an antitussive preparation, and dextromethorphan are on the market. The main synthetic substances which have shown antitussive activity are : methadone, D-methadone, D-isomethadone, 6-dimethylamino-4,4-diphenylhexanone, dextromethorphan.

REFERENCES

1. Eisleb, O. & Schaumann, O. (1939) *Deutsch med. Wschr., 65,* 967.
2. Germany, Patent No. 679281.
3. Small, L. F. & al. (1938) *Publ. Hlth. Rep.* (Wash.), Suppl. No. 138.
4. Schaumann, O. (1940) *Arch. exp. Path. Pharmacol, 196,* 109.
5. United States of America, Office of the Publication Board, Department of Commerce, Report No. P.B.981, p. 85.
6. Scott, C. C. & Chen, K. K. (1946). *Pharmacol., 87,* 63.
7. World Health Organization (1949), *Official Records of the World Health Organization,* No. 19, p. 32.
8. World Health Organization, *Techn. Rep. Ser.* 1950, No. 21.
9. World Health Organization, *Techn. Rep. Ser.* 1952, No. 57.
10. World Health Organization, *Techn. Rep. Ser.* 1954, No. 76.
11. World Health Organization, *Techn. Rep. Ser.* 1955, No. 95.
12. World Health Organization, *Techn. Rep. Ser.* 1956, No. 102.
13. Permanent Central Opium Board, *Report to the Economic and Social Council on the Work of the Board in 1955,* Geneva 1955, Doc. No. E/OB/11.
14. Eisleb, O. (1942) *Med. Chem.* 4, 213.
15. Cahen, R. L., Epstein, H. J. & Krementz, C. S. (1948) *J. Pharmacol. 94,* 328.
16. Drug Supervisory Body, *Estimated World Requirements of Narcotic Drugs in 1956,* Geneva 1955, Doc. E/DSB/13.
17. United Nations, Economic and Social Council, *Official Records, Eighteenth Session* (1954), Doc. No. E/2654.
18. Berger, L., Ziering, A., & Lee, L. (1947) *J. Org. Chem. 12,* 904.
19. Gross, E. G., Holland, H. L. & Schueler, F. W. (1948) *J. appl. Physiol., 1,* 298.
20. Leimbach, D. G. & Eddy, N. B. (1954) *J. Pharmacol., 110,* 135.
21. Eddy, N. B. & al. (1950) *J. Pharmacol., 98,* 121.
22. Fromberg, K. (1951) *Arch. int. Pharmacodyn., 85,* 387.

The Problem of Morphine Synthesis

By David Ginsburg, Israel Institute of Technology, Haifa, Israel.

The techniques used by the organic chemist to elucidate the constitution of a given molecule of simple or complex structure are, in principle, the same. After the compound under investigation is isolated in pure form and its empirical constitution is established by elementary analysis, the organic chemist applies degradative chemical reactions in which he chops the molecule into simpler fragments whose constitution it is easier to determine. The degradative technique allows one to reason from the structures established for the simpler fragments and from prior chemical knowledge, and thus deduce which structure would seem reasonable for the original, more complex molecule.

It is clear that the new tools available to the organic chemist, particularly those of ultraviolet and infrared spectroscopy, make the task — once so formidable — of determining the structure of a complex molecule simpler in the present generation. It could be said that infrared spectroscopy has supplied the average chemist today with an additional pair of eyes. True, it has not made a genius out of him, but it has revolutionized the technique of organic chemistry, and the average chemist today can accomplish more than his average counterpart in the previous generation. Further, he can carry more complex problems to their successful solution, not only because of the availability of these physical tools, but because of the obvious progress in his field due to his predecessors of the previous generations.

The organic chemist is not satisfied with the assignment of a structure to a molecule, no matter how logical his deductions may seem on the basis of the degradative evidence. Unsuspected rearrangements may have occurred during degradative reactions. Fine stereochemical points may still be obscure, and fully convincing deductions are sometimes impossible until synthesis of the molecule has been accomplished through a series of known reactions from compounds of unequivocal structure. Such an approach should appeal to the pure logician. It is unfortunate, however, that the organic chemist cannot always fulfil the rigid demands of his self-imposed logic during his lifetime. With certain complex structures several life-spans may elapse between isolation and final synthesis. In some cases, new and unprecedented reactions may creep into the complex synthesis, thus somewhat tarnishing the purity of the required logical discipline.

The morphine story is a good case in point and can be used as a case-history to illustrate the above statements.

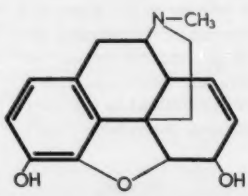
Morphine was first isolated by Sertürner in 1805. In 1925, Gulland & Robinson summarized the results of a century of degradative work and proposed the correct formulation of the alkaloid. The circle was completed in 1952, when Gates and his co-workers succeeded in synthesizing this complex molecule. On the heels of this first synthesis of morphine, a second synthesis was published in 1954.

Since the syntheses of morphine by both the Gates group and the Ginsburg group include steps which were at least partly unexpected, the rigid logician might be doubtful as to whether the stamp of final approval should be placed on the closure of the morphine story. However, the organic chemist who is aware of the trials and tribulations involved in the degradation and synthesis of complex natural products, is usually more charitable than the rigid logician and accepts morphine into the ranks of substances whose structure is unequivocally established.

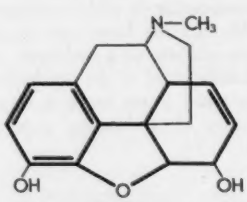
Now, when we inspect the Robinson formula for morphine, we are prejudiced through our human frailty, by our previous fields of interest. We look at the spatial configuration of the morphine molecule from different vantage points and from different angles.

The chemist who is primarily interested in steroids sees morphine as a steroid which has somehow gone astray. Three of the four rings present in the steroid molecule are present in morphine, but ring D has disappeared and has been replaced by a piperidine ring fused to the carbocyclic system in an unorthodox way. Yet the reactions of certain morphine derivatives are analogous to those of steroids (cf. bromination of coprostanone and dihydrothebainone (1)).

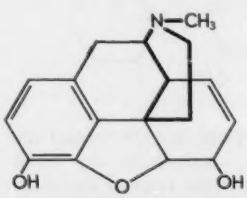
The chemist working in the field of polycyclic aromatic compounds will certainly note the reduced phenanthrene system present in morphine. The furan chemist will observe that morphine is a furan or a reduced dibenzofuran derivative. The chemist interested in piperidine derivatives will not fail to note the N-methyl piperidine portion of the morphine molecule. Indeed, it was only when this viewpoint was taken that the synthetic compounds based on the morphine structure began to have analgesic activity. The chemist interested in isoquinolines will observe that morphine can be viewed as an isoquinoline derivative. When biogenetic arguments are brought into play, one can see that a substituted 1-benzylisoquinoline portion is present in the morphine molecule.



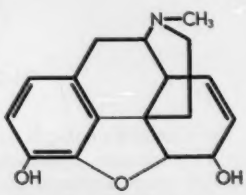
Hydrophenanthrene formula



Reduced dibenzofuran formula



N-methylpiperidine formula



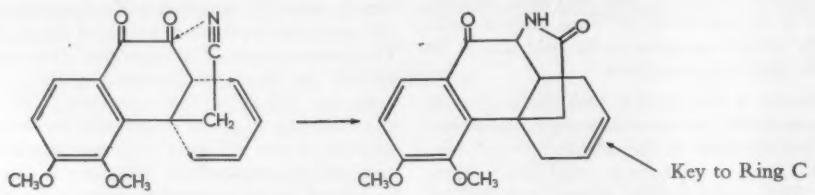
l-Benzylisoquinoline formula

One cannot under-estimate the importance of the various viewpoints, angles of observation and vantage points. It cannot be a coincidence that the Gates synthesis of morphine involves a naphthaquinone starting material when one knows of the earlier association between Dr. Gates and Professor Fieser. Grewe has published an excellent article (2) on the biogenetic considerations (first pointed out by Robinson (3)) which led him to the synthesis of N-methylmorphinan. The latter synthesis has been described in a beautifully written series of papers (4) which should be made required reading for all graduate students of organic chemistry. The interest of Koelsch in the Michael condensation led him to apply this reaction to the synthesis of morphine, thus far culminating in the synthesis of N-methylmorphinan (5). Surely it is no original discovery that persons of varied chemical interests apply their expert knowledge in specific fields and attempt to extend it to other fields.

It is not necessary to give a full review of the many varied approaches to the morphine structure, as this field has been reviewed recently (6). Certain developments in the field have nevertheless rendered some aspects of the recent review obsolete. Therefore, several of the more successful approaches will be discussed here in a general way. The details of each synthetic route may be obtained by consulting the original publications.

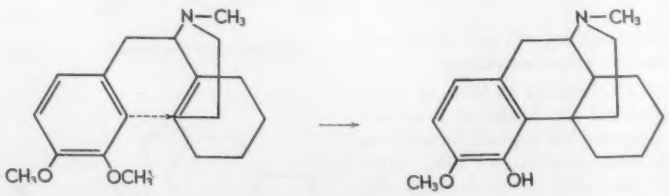
The Gates synthesis (7) may be termed the naphthalene approach. Rings A and B of morphine are preformed in a suitably chosen naphthalene derivative which bears in the 4-position the embryo of the piperidine ring. Ring C is attached through a Diels-Alder reaction. The piperidine ring forms " of its own accord ". The latter phrase is placed in quotation marks because most organic chemists will accept the adage that " God helps those who help themselves ".

Professor Woodward made a statement at the recent Gordon Conference on Steroids and Related Natural Products (8) which I am taking the liberty of paraphrasing : "lucky " cyclizations take place when groupings are so placed by the synthetic chemist that Lady Luck is in a favourable position to exert her influence. It is clear that it was not by chance that Gates placed a cyanomethyl group at the 4-position of his naphthaquinone starting material. Once the tetracyclic ring system present in morphine had been prepared, the synthesis of morphine was, in principle, certain to succeed. I do not wish to under-estimate the subsequent steps of the Gates synthesis, the execution of which was brilliant. The major factor, however, is that a double bond was present in ring C, designed to be present as the key or the wedge for insertion of other groups necessary to convert the first tetracyclic intermediate of *trans-* stereochemistry to the final goal — morphine. Knowledge of various reactions and electronic mechanistic principles certainly helped in the final stages, but the point I wish to make is that the beauty of the Gates synthesis is in starting from a very well chosen set of materials which already has built in the features for further synthetic elaboration — the nitrogen atom for the piperidine ring and the double bond resulting from the diene reaction in a position to serve as key for the introduction of further necessary features into the molecule.



The Grewe synthesis of N-methylmorphinan and tetrahydrodesoxycodeine (4) follows the presumed biogenetic route used by the opium poppy. The starting materials are compounds of which analogues are present in the plant, and although the latter uses enzyme systems to accomplish the key addition of a hydrogen atom of the benzene ring to the double bond of the octahydroisoquinoline intermediate, it is necessary to use much more stringent conditions in the laboratory (long heating with concentrated phosphoric acid).

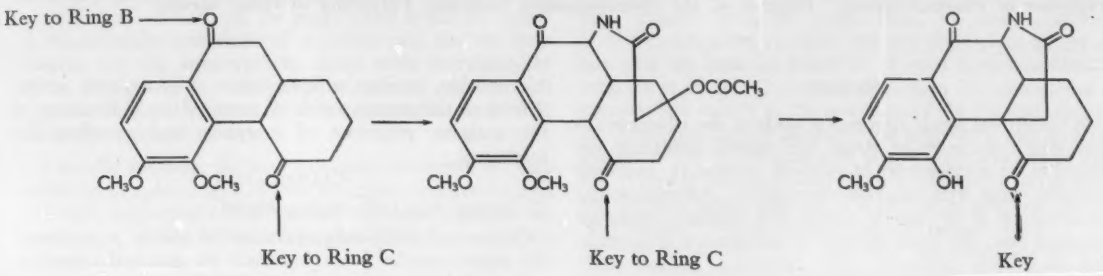
The difficulty in the Grewe approach lies in preparing suitable intermediates for preparing morphine itself. A key to ring C is lacking. Despite the fact that Grewe and his associates did not synthesize morphine itself, they were the first to construct the tetracyclic skeletal system present in morphine and to demonstrate the identity of their synthetic tetrahydrodesoxycodeine with that of the product derived from natural sources by various degradative reactions.



The Ginsburg approach to morphine may be termed the phenylcyclohexane approach. In contrast to the Gates method which constructs the carbocyclic rings of morphine from AB+C, this approach starts with AC and adds on B.

The nitrogen atom required for the piperidine ring is either present in the grouping which enters the AC system through Michael addition, or is introduced subsequently into the ABC system by the use of a carbonyl group acting as the key to

ring B. Here also the nitrogen containing ring is cyclized through an unprecedented reaction, made possible, however, by the presence of a second carbonyl group whose function it is to serve as a key to ring C. The synthesis culminates with dihydrothebainone since this ketone was previously converted to morphine by Gates and his associates. Again, the success of this approach can be traced to the presence of activating groups at points required for further synthetic elaboration. A somewhat similar approach by Horning and associates (9) failed because such keys were lacking. The same may be said for the Fieser-Holmes AB + C approach (10) preceding the Gates work, in which groups introduced as potential keys failed to turn the lock.



In their present stage of development, neither of the two published syntheses of morphine is practical from the commercial point of view. The Grewe approach has been modified and various synthetic analgesics are being manufactured and marketed, e.g., 3-hydroxy-N-methylmorphinan. The major importance of work done on the synthesis of a complex molecule does not lie merely in the successful achievement of the synthesis. The fun involved in the work should not be under-estimated; nor should the satisfaction in successful completion of a long and difficult road. Surely the major importance lies in the development and application of synthetic methods and in the cross-fertilization of different fields of research in organic chemistry. In general, the more complex the molecule under attack, the broader the interest and the more numerous are the theoretically possible approaches and vantage points. The true value of a synthesis of a complex molecule is not merely in the completion of the circle of organic chemical logic which requires the structure deduced by degradation to be proved by synthesis, but in the application to other fields of the progress made through that synthesis.

References

1. Ginsburg, *U. N. Bulletin of Narcotics*, 1954, VI : 1, p. 32.
2. Grewe, *Naturwiss.*, 1946, *33*, 333.
3. Robinson, *Proceedings Univ. Durham Phil. Soc.*, 1927-1928, *8*, part 1, 14.
4. Grewe, *et al.*, *Ber.*, 1948, *81*, 279; *Ibid.*, 1951, *84*, 527; *Ann.* 1949, *564*, 161.
5. Koelsch & Albertson, *J.A.C.S.*, 1953, *75*, 2095.
6. Stern, *Quart. Rev.*, 1951, *5*, 405.
7. Gates, *et al.*, *J.A.C.S.*, 1948, *70*, 2261; *Ibid.*, 1950, *72* : 1141, 4839; *Experientia*, 1949, *5*, 285; *J.A.C.S.*, 1952, *74*, 1109.
8. New Hampton, New Hampshire, 6 August 1954.
9. Horning, *et al.*, *J.A.C.S.*, 1948, *70*, 2072, 2941, 2945; *Ibid.*, 1949, *71*, 1359.
10. Fieser & Holmes, *J.A.C.S.*, 1936, *58*, 2319; *Ibid.*, 1938, *60*, 2548.

Natural and Synthetic Drugs with Morphine-like Effects Considered from a Pharmacognostic[1] Point of View

By Arnold Nordal, Ph.D.
Professor of Pharmacognosy. Director of the Pharmaceutical Institute, University of Oslo, Norway

SYNOPSIS

In the present article reference is made to the all-important part which the study of drugs and natural substances has played in the development of synthetic substances, including synthetic drugs with morphine-like effects. Advantages and disadvantages in the use of natural and synthetic drugs are discussed from the point of view of therapeutics, economics, and production technique. The subsequent section refers to the predominant role of the poppy plant in the world's production of morphine and morphine derivatives. Then follows a critical examination of the various drugs.

Definitions and Terminology

Morphine belongs to a large group of drugs designated in pharmacology as narcotics. In therapy a distinction is usually made between four principal types of narcotic—(1) *analgesics* (pain-killing drugs), (2) *hypnotics* (sleep-inducing drugs), (3) *sedatives* (soothing drugs) and (4) *anaesthetics* (drugs inducing unconsciousness). The lines of demarcation between these groups are not clearly drawn, and depend usually in part on the size of the dose.

Administered in proper doses and at the appropriate time, morphine can act either as a sedative, as a hypnotic, or—particularly in combination with other drugs—as an anaesthetic (for example, morphine-scopolamine in basal narcosis). Nevertheless, its most striking feature is its analgesic action. Therefore the present article is restricted to a discussion of the analgesic properties of morphine and morphine-like substances.

[1] Pharmacognosy is the study of crude medicinal drugs—i.e., the raw materials of vegetable and animal origin which are used directly for medicinal purposes or in the manufacture of pharmaceutical preparations.

CLASSIFICATION

(1) *Natural drugs with morphine-like effects*

Opium and medicinal preparations of opium, poppy straw (or poppy capsules), morphine and the principal secondary opium alkaloids.

(2) *Semi-synthetic drugs with morphine-like effects (derivatives of opium alkaloids)*

For example : Benzylmorphine (peronine), ethylmorphine (dionine), diacetylmorphine (heroin), dihydrodesoxymorphine-D (desomorphine), ethyldihydromorphinone, methyldihydromorphinone, (metopon), monoacetylmorphine, α-isomorphine, β-isomorphine, γ-isomorphine, tetrahydroxydesoxymorphine, dihydromorphinone (dilaudid), allopseudocodeine, heterocodeine, isocodeine, pseudocodeine, dihydrocodeinone (dicodid), dihydrohydroxycodeinone (eucodal), morpholinylethylmorphine (pholcodin).

(3) *Synthetic drugs with morphine-like effects* (4)

For example, representatives from the pethidine group, the methadone group, the morphinan group and the dithienylbutenylamine group.

The substances from these groups are prepared exclusively by synthesis from common chemicals not related to the poppy plant.

A. GENERAL DISCUSSION

1. NATURAL SUBSTANCES AS PATTERN FOR SYNTHETIC DRUGS

Our modern science of drug therapy is built upon centuries of empirical knowledge and scientific research.

Through experience and tradition a large number of the substances used in modern medicine have been used in much the same way for centuries by primitive people throughout the world. This is true of important substances such as opium, digitalis, quinine bark, coca leaf, ergot, curare and rauwolfia, to mention but a few.

One of the first scientists who devoted his attention to a closer study of the active principles of the crude drugs was Paracelsus (1493-1541). He attempted through distillation, pyroanalysis and other alchemical processes to isolate the "quintessence"—the active principle—of opium. His crude methods failed to produce results; but he had shown the way, and other men of science in turn tackled the same problems more successfully. The introduction by the pharmacist C. W. Scheele of crystallization as a method for the purification of natural substances was of fundamental importance in this development.

The isolation of the active components of drugs in pure crystalline form paved the way for accurate analyses of their chemical structure and pharmacodynamic effect, and thereby also directly influenced the development of the synthesis of new drugs.

The chemical transformation and gradual breaking down and re-synthesis of the natural substances of medicinal value, combined with pharmacological research, provided valuable information about the relationship between chemical structure and pharmacological effects. As will be seen later, similar studies of the structure of morphine were also of great importance for the development of a series of synthetic morphine substitutes.

2. Natural and synthetic drugs, advantages and disadvantages

(a) *The Therapeutic Aspect*

In the case of drugs with morphine-like effects the choice between the natural substances and synthetics goes back only a couple of decades. Although morphine and some of the secondary alkaloids of opium can now be synthesized by organic chemical methods, the poppy plant is still the source of commercially manufactured morphine and also the basic material for the semi-synthetic drugs with morphine-like effects (cf. group 2). With the morphine substitutes of synthetic origin (cf. group 3) it is quite different, as they are totally artificial substances.

Generally speaking, the new morphine substitutes are very similar to morphine, both in their analgesic effect and in their addictive properties. The method of their manufacture, however, is widely different from that of the corresponding natural substances. As a result of the synthesis of new substances, the range of preparations with morphine-like effects is now wider and more varied than it was in former years, as none of the morphine substitutes produces exactly the same effects or, more accurately speaking the same side-effects. The physician's choice of an analgesic for the treatment of various cases is often determined by the nature of these side-effects. For example, although pethidine has weaker analgesic properties than morphine, this drug is generally preferred to morphine for biliary or renal colic because of its pronounced spasmolytic properties.

From the standpoint of practical therapy, the new synthetic drugs offer wider therapeutic possibilities than the natural drugs, and therefore call for further development. On the other hand, it cannot be denied that a steadily growing number of physicians, healers and the general public view with concern the increasing use, both in therapy and in our daily diet, of synthetic substances alien to human cells (23).

One of the determining factors in the physician's choice of an analgesic is the centuries-old body of tradition underlying the use of opium therapy throughout the world. Opium and opium preparations are still officinal medicaments in the pharmacopoeias of all countries, and in many instances physicians, guided by clinical experience, choose opium extracts or compounds of pure alkaloids in preference to morphine itself or synthetic morphine substitutes.

(b) *The Economic Aspect, the National Economy and Production Technique*

The great advantage of synthetic chemistry is its almost limitless capacity for producing chemical and therefore pharmacodynamic variants. On the other hand, the synthesis of medicinal preparations requires a certain degree of technical skill which is not yet available in all parts of the world.

A minimum of technical apparatus is required to manufacture analgesics from the poppy plant. In many countries with a rudimentary chemical industry the opium poppy is now and has been for hundreds of years a well-established crop. It is often an important element in the economy of a country, not merely as the raw material for the manufacture of opium and opium alkaloids, but frequently, and to a far greater extent, as the source of poppy seeds and poppy-seed oil. There is little likelihood that the cultivation of the poppy for these latter purposes will decline or disappear in the near future. If these countries were to turn to imported synthetic analgesics instead of using their own available sources of supply, they would be following an unsound economic policy.

(c) *The Social Aspect*

It is well known that the production of opium and the accompanying smuggling and abuse of the drug give rise to a series of social problems with serious and far-reaching implications. Various countries have attempted to cope with the evil by prohibiting the cultivation of the poppy plant, and to find an alternative solution to the analgesic problem partly through the import of opium and opium alkaloids and partly through the synthesis of morphine-like substances under strict national control. Obviously a policy of this kind may to some extent solve the problem as it affects a particular country, but not the international problem. As stated above, the cultivation of the poppy plant and the production of opium are so closely connected with the needs of national economies that a total prohibition of the cultivation of the opium poppy throughout the world at the present time would have serious economic consequences.

If there were a sudden change-over from the use of natural drugs to the use of synthetics, the normal outlets for opium would be suddenly reduced. Quantities of opium which could not be disposed of would sooner or later in all probability find their way into the illicit traffic, and the opium-producing countries would consequently be faced with a grave problem.

B. SPECIFIC DISCUSSION

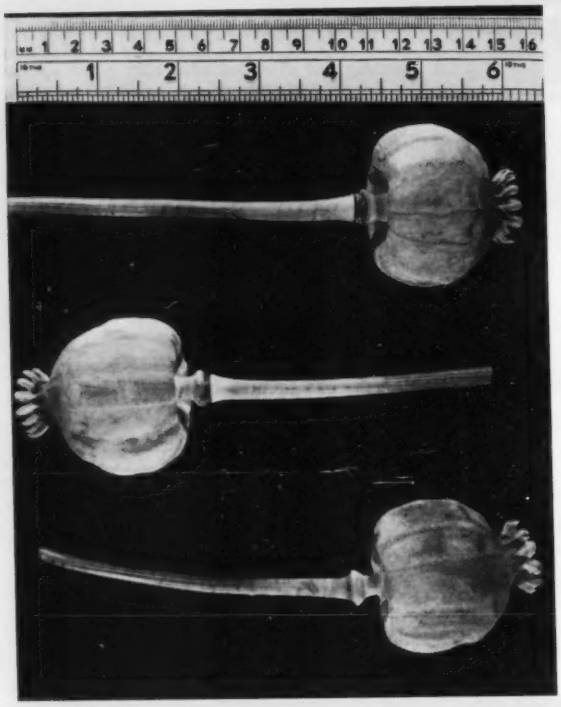
1. The poppy plant, its present uses and future prospects

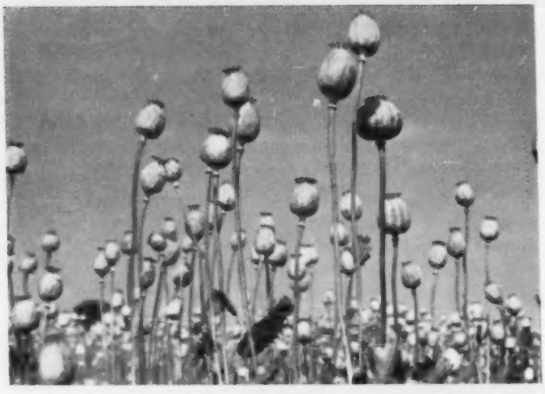
Today there are a great many known varieties and subspecies of the opium poppy, *Papaver somniferum L. Papaveraceae*. History shows that it is one of the world's oldest cultivated plants. This is also obvious from the fact that the plant is no longer found in a wild state. Most of the world's utility plants are more or less confined to a definite climate and within relatively narrow geographical limits. This is not the case with the opium poppy, which can be successfully grown in relatively large areas of the world with a high yield of opium alkaloids (11). (cf. Fig. 1 and 2). It does not require any particular type of soil and reacts well to fertilizers. This is one of the main advantages in terms of agronomics, national economy and the available supply. As will be seen from the following diagram (Table I) several important industries all over the world are dependent on the opium poppy.

The world production of opium reported to the Permanent Central Opium Board amounted to 1,291 tons in 1953 (26). The annual world production of poppy seeds amounts to several thousand tons.

Today only a small fraction of the opium poppy grown throughout the world is used for production of opium and opium alkaloids.

The opium poppy each year provides employment and a livelihood for a very large number of people in all its related





Opium poppy grown in Norway.

industries and trades. Moreover, the world economy does not yet by any means exploit its potentialities to the full. The principal reason for this is to be found partly in governmental restrictions (cf. the Opium Poppy Control Act, 1942, which prohibits cultivation of the opium poppy in the United States without a licence), and partly in irrational operating methods dictated by tradition. The classical method of extracting opium (incising the capsule and gathering the dried latex) utilizes only a fraction of the plant's total alkaloidal content. The rest remains in the straw and the capsules which are mostly burnt or left to rot away. The method is based on almost two thousand years of tradition and is gradually being replaced by methods which require less human labour.

A large proportion of all the opium produced is used for the extraction of opium alkaloids. It immediately becomes obvious that when alkaloids are the end product, the intermediate stage of producing opium is an unnecessary expense.

Recognition of this fact is now becoming general, and the manufacture of opium alkaloids from poppy capsules and poppy straw is growing in certain countries, especially in eastern Europe. For example, 8 tons of morphine were manufactured from poppy straw in 1946, 17 tons in 1952, and 19 tons in 1953. In other words, in 1953 approximately one-quarter, in 1952 one-fifth and in 1946 one-sixth of all morphine manufactured was extracted from poppy straw (20).

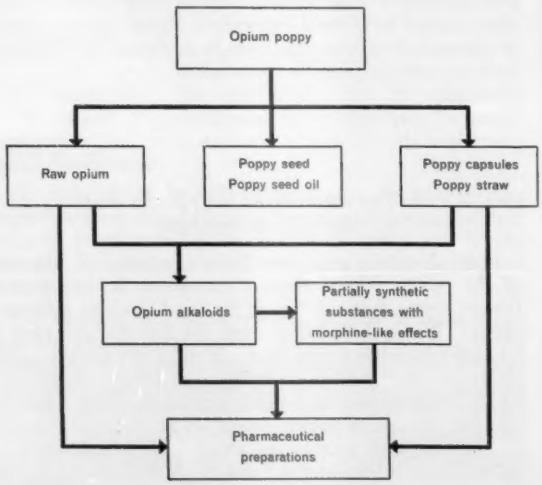
The extraction of morphine according to this principle has long been dependent upon the development of practicable, economical methods. Today this problem has been solved in principle (3), and new and improved methods are constantly being developed.

The future prospects of the poppy plant seem to be closely linked to the following conditions, to mention but a few : (1) an expanded manufacture of opium alkaloids from the poppy plant itself (cf. above); (2) the development of new varieties of the opium poppy; (3) a steady and preferably increasing use of opium alkaloids. The last condition depends in part on the continued development of synthetic morphine substitutes and on whether science will succeed in manufacturing drugs free from the undesirable side-effects of morphine—primarily that of addiction. Research along this line is now in progress (29).

The development of new varieties of the opium poppy should probably be planned with a dual purpose—(*a*) to develop varieties with a higher alkaloidal content than is found today in plants grown for both alkaloids and seeds; [2] (*b*) to develop plants with a low alkaloidal content or none at all, exclusively for seed production (cf. C. C. Fulton, p. 82).

[2] This type of poppy would probably have to be grown under supervision.

Table I



The results obtained with the quinine tree *Cinchona species* demonstrated clearly that it is now possible to double the alkaloidal content of a plant. It would therefore not be unreasonable to assume that the alkaloidal content of the opium poppy can also be altered in one way or another. The methods formerly used by Dutch scientists in developing the quinine tree were primarily selection and crossing. In addition to these classical methods, there are today a number of new ones which have already produced noteworthy results in the cultivation of drug-producing plants. I refer particularly to polyploidys and the modern mutation methods using various rays (neutron rays in uranium piles, X-rays, ultra-violet rays and the like). The former method has been used particularly on higher types of plants, the latter on lower organisms, for example in the development of new strains of moulds and actinomycetes, etc., in the production of penicillin and other antibiotics.

The poppy plant contains the same alkaloids as opium (cf. below) but in much smaller quantities.

According to Wüest and Frey (11), the morphine content of poppy capsules varies between 0.18 and 0.89 per cent, with an average of 0.37 to 0.53 per cent. The results of analyses of the morphine content of the stalks differ greatly, some reports showing between 0.01 and 0.05 per cent and others from 0.10 to 0.15 per cent (11).

2. Opium

Opium, the air-dried milky exudation obtained by incising the unripe capsules of *Papaver somniferum L.*, is produced in many temperate and subtropical regions. It has been found to contain approximately twenty alkaloids, which together make up about twenty per cent of its weight.

Henry (14) divides the alkaloids of opium into the following five categories :

(1) *Tetrahydroisoquinoline derivatives*, comprising Hydrocotarnine, $C_{12}H_{15}O_3N$;

(2) *Benzylisoquinolinederivatives*—e.g., Papaverine, $C_{20}H_{21}O_4N$, Narcotine, $C_{22}C_{23}O_7N$, Narceine, $C_{23}H_{27}O_8N$;

(3) *Cryptopine type*—e.g., Cryptopine, $C_{21}H_{23}O_5N$;

(4) *Morphine type*—e.g., Morphine, $C_{17}H_{19}O_3N$, Codeine, $C_{18}H_{21}O_3N$, Thebaine, $C_{19}H_{21}O_3N$, Porphyroxine, $C_{19}H_{23}O_4N$;

(5) *Alkaloids of unknown constitution*

The approximate percentage contents of the six alkaloids found in the largest quantities are, according to Fulton (11), the following :

Morphine, 3 to 23 per cent;
Narcotine, 1 to 11 per cent;
Codeine, from several tenths of 1 per cent up to 4 per cent;
Thebaine, from several tenths of 1 per cent up to 4 per cent;
Papaverine, from a few tenths of 1 per cent up to 2 per cent at least;
Narceine, from 0.1 per cent or so, probably up to 1 per cent.

Although intensive research has been carried out for centuries to ascertain the chemical composition of opium, much remains to be done before that goal is achieved. This point was also emphasized strongly in a recent article in the *Bulletin on Narcotics* (5).

The pharmacopoeias require medicinal opium to be prepared with a fixed morphine content, usually approximately 10 per cent. It should here be kept in mind that the various assay methods can give widely differing results (1, 14).

It is particularly important in this connexion to make clear the great significance of opium in modern therapy and the existing possibilities of replacing it with synthetic drugs. A study of the components of opium clearly shows it to be a product with a complex structure. Besides the active principle, morphine, a characteristic pharmacodynamic effect has also been observed in a number of the secondary alkaloids (18, 22). A synergistic or antagonistic relationship has also been found to exist between the various alkaloids (18), and it has been possible to demonstrate that even the nitrogen free ballast components influence absorption from the intestine and thus the effectiveness of the drug. Accordingly, opium cannot yet be replaced by any single synthetic substance.

The other problem which still remains to be discussed is the role which opium plays in modern therapy and as a raw material for pharmaceutical preparations. Opium is included in all modern pharmacopoeias, and a large proportion of all the medicinal opium produced is used in the manufacture of galenical preparations such as *Pulvis antasthmaticus*, *Pulvis Cynoglossi compositus*, *Pulvis Ipecacuanhae opiatus*, *Extractum Opii siccum*, *Tinctura Opii*, *Tinctura Opii Camphorata*, *Tinctura Opii Crocata*, and the like. In this connexion also, the mixture of opium alkaloids should be mentioned.

In 1909 *Sahli* introduced into medicine under the name of pantopon (15), a preparation containing all the alkaloids of opium in the form of hydrochlorides. Preparations of this type (often simplified to include morphine salts and some of the most important secondary alkaloids of opium in a fixed proportion) are used today all over the world. As compared with aqueous or alcoholic extracts from opium, preparations of the pantopon type have the great advantage that they can be used for injection. Many years of clinical experience have also shown that these compounds have a different effect on the central nervous system from that of morphine itself. Thus they are not so likely as pure morphine (18, 22) to produce unpleasant side-effects such as nausea and vomiting. This illustrates the advantages often found in natural mixtures of compounds over simple chemical individuals. In this connexion it should be remembered that many of the pantopon-like preparations are merely mixtures of isolated pure opium alkaloids in the proportion in which they occur in Turkish opium (cf. Pharm. Helv. 1933, Pharm. Suec. 1946, Pharm. Dan. 1948).

It may therefore be concluded that opium and opium preparations still play an important role in modern therapy.

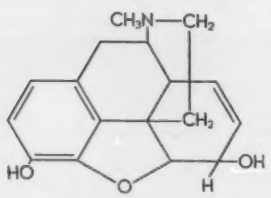
As has already been stated, the chemistry and pharmacology of the opium alkaloids are stillto a certain extent unknown, and they thus offer a rich field for future chemical and medical research.

3. Poppy capsules (fructus papaveris)

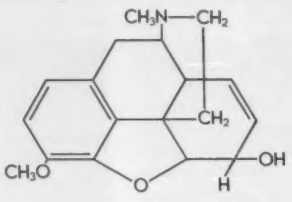
The unripe capsules of the opium poppy were formerly included in a number of pharmacopoeias under the designation *Fructus Papaveris immaturus*. The drug was used largely in the manufacture of poppy syrup (*Syrupus Papaveris*), a preparation which was well known for its effectiveness in keeping young children—even infants—quiet at night. (Bearing in mind the unhealthy effects of morphine on young children, this may be cited as an example of the dubious therapy of the past.) Since the alkaloidal content of poppy capsules is consi-

Table II

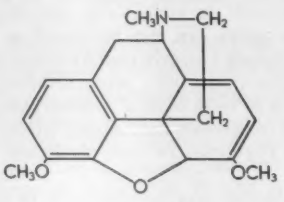
THE PRINCIPAL OPIUM ALKALOIDS



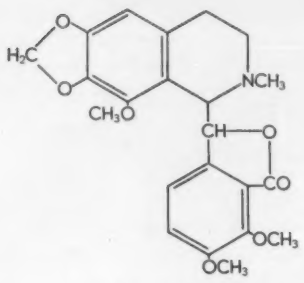
(II-1) — *Morphine*



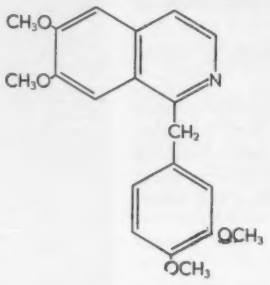
(II-2) — *Codeine*



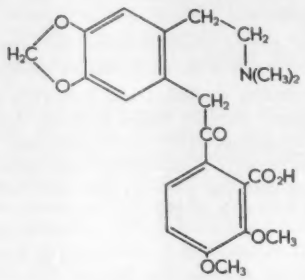
(II-3) — *Thebaine*



(II-4) — *Narcotine*



(II-5) — *Papaverine*



(II-6) — *Narceine*

derably higher than that of the other parts of the plant, this drug is popular today as a raw material for the manufacture of opium alkaloids by extraction (3).

4. MORPHINE (cf. table II-1)

The isolation of morphine by Derosne (15) in 1804 and the discovery of its basic character by Sertürner (15) in 1817 were of epoch-making importance not only for the development of the chemistry of alkaloids, but also for extensive studies of the active principle of opium.

These studies, which have been in progress for 150 years and are in fact still going on, made possible the improvement of morphine through the manufacture of derivatives, the determination of the chemical structure of morphine, the manufacture of synthetic substances with morphine-like effects, and culminating in the total synthesis of morphine, which was accomplished by Gates and his co-workers (12) in 1950-1952 on the basis of preparatory studies by Grewe and his co-workers (13).

Although morphine is a natural substance and also the most important representative of the natural analgesics, its total chemical synthesis is of great interest in this connexion. The question naturally arises : what effect will the chemical synthesis of morphine have on the present world supremacy of the opium plant as a source of morphine? This question is difficult to answer at present, as it is too early to form a reliable opinion. That will depend not only on the ability of the synthetic products to compete in the morphine market, but also—and in at least equal measure—on such factors as the needs of national economy as reflected in trade agreements, customs barriers and the like. At the present time, however, there seems to be no indication that the synthesis of morphine can have any practical value in morphine production.

The main part of all morphine manufactured is used for conversion into codeine and other morphine derivatives.

5. THE SECONDARY ALKALOIDS OF OPIUM (cf. table II-2 to 6)

The five secondary alkaloids which are of medical and economical importance in opium are codeine (II-2), thebaine (II-3), narcotine (II-4), papaverine (II-5) and narceine (II-6).

Papaverine was synthesized as early as 1909 by Pictet & Gams (15). In the following year narcotine was synthesized by Perkin & Robinson (15). Narceine can be prepared from narcotine. The complete synthesis of morphine and codeine by Gates (12) and his co-workers has also made the total synthesis of thebaine possible. Except for the partial synthesis of codeine from morphine, the aforesaid syntheses have little or no practical significance nowadays, for the other substances are obtained as by-products of the manufacture of morphine from opium or opium derivates.

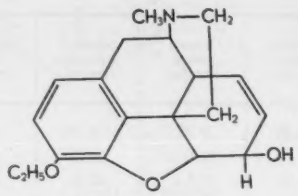
As mentioned above, the secondary alkaloids in medicinal opium seem to intensify the analgesic effect of the morphine (18), and, as will be shown below, some of them have greatly influenced the development of the semi-synthetic morphine substitutes in the next group. Papaverine is one of the most potent coronary vasodilator agents, and narcotine has recently been found to possess marked cough depressing properties.

6. SEMI-SYNTHETIC SUBSTANCES WITH MORPHINE-LIKE EFFECTS (*derivatives of opium alkaloids*)

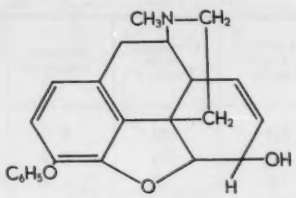
Although morphine in appropriate doses relieves any pain, it is not by any means the ideal analgesic. Among the most

Table III

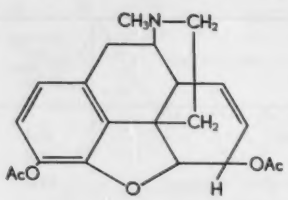
DERIVATIVES OF OPIUM ALKALOIDS



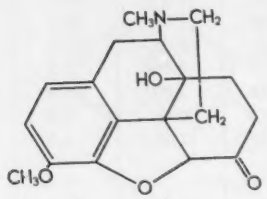
(III-1) — *Dionine*



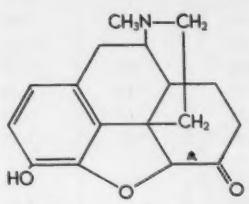
(III-2) — *Peronine*



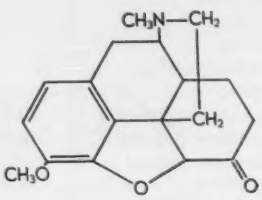
(III-3) — *Diacétylmorphine*



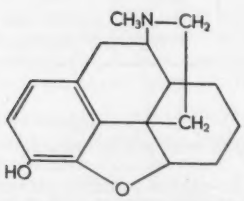
(III-4) — *Eucodal*



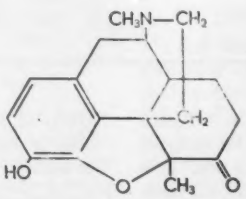
(III-5) — *Dilandid*



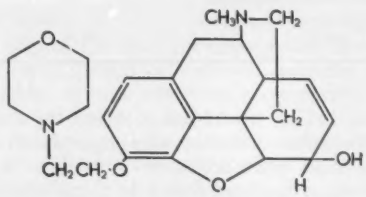
(III-6) — *Dicodide*



(III-7) — *Desomorphine*



(III-8) — *Metopon*



(III-9) — *Pholcodine*

conspicuous undesirable side-effects (6) are a depressive effect on the respiratory centre, nausea and vomiting, constipation and serious addiction liability. It is also rather toxic.

There has therefore been no lack of attempts to " improve " morphine and other opium alkaloids by producing derivatives from them (18). When the chemical and pharmacological relationship between morphine and its methyl ether (codeine) became known (codeine has a lower addiction liability than morphine), attempts were made to exploit this discovery by producing its ethyl ether (dionine, III-1) and its benzyl ether (peronine III-2).

In addition, a number of isomers of codeine, such as pseudocodeine, isocodeine and allopseudocodeine, were prepared and tested. These substances produce an effect similar in kind to that of morphine, but are less powerful analgesics. On the other hand, some of the primary alkaloid's characteristic effects are intensified.

Acetylation of both the hydroxyl groups in morphine yielded a substance (diacetylmorphine, III-3) which was introduced into therapy as early as 1898 under the name of heroin. While heroin has a considerably stronger analgesic action than morphine, its addiction liability is also much greater.

By a rather simple chemical process thebaine is converted into dihydrohydroxycodeinone (eucodal, III-4), a substance that has approximately the same analgesic effect as morphine, but is less likely than morphine to provoke nausea and vomiting.

Great therapeutic interest was centred on certain morphine derivates prepared by Skita and his co-workers in the German firm of Knoll, Ludwigshafen, in the period 1910-1918 (18). By a special process of hydration and isomerization, dihydromorphinone (dilaudid, III-5) was obtained, the methylation of which yields dihydrocodeinone (dicodide, III-6). Möller (22) says of these substances : " As a rule, laudacon (dilaudid) has no therapeutic advantages over morphine. It is *indicated* in cases in which a powerful analgesic effect is desired but in which morphine would be particularly stupefying or cause undesirable side-effects. It must be used with the same caution as morphine. " According to the same author, dicodide is intermediate between codeine and morphine both in its action and in its addiction liability.

A large-scale systematic study of morphine substitutes was carried out between 1930 and 1940 by the Committee on Drug Addiction of the United States National Research Council (27). The primary purpose of the study, which was directed by Small & Eddy, was to find morphine substi-

Table IV

PHARMACOLOGICAL EFFECT OF SOME MORPHINE DERIVATIVES

Alkaloidal base	*Formula No. (cf. tables II-III)*	*Toxicity LD50 (mg./kg.)*	*Convulsant action (mg./kg.)*	*Analgesia (mg./kg.)*	*Exciting effect (mg./kg.)*	*Emetic action (mg./kg.)*	*General depression (mg./kg.)*	*Respiratory effects (mg./kg.)*
Morphine	II-1	531	531	0.75	0.57	0.22	6.75	0.15
Codeine	II-2	241	161	8.04	8.04	16.0+	36.1	1.3
Ethylmorphine (Dionine)	III-1	136	122	7.66	17.0	8.5+	42.6	0.48
α—Isomorphine		890		0.80	0.89	0.13	22.2	0.15
Isocodeine		589	589	13.0	13.0		58.9	1.5
β—Isomorphine		324	324	10.1	9.26	4.63	74.0	2.14
Allopseudocodeine		267	178	13.3	26.7	13.3+	80.1	
γ—Isomorphine		2,000+		7.09	7.09	1.77	133+	2.36
Pseudocodeine		1,780		17.8	22.2	4.45	89.1	48.0
Monoacetylmorphine		293	180	0.18	0.18	0.18+	0.9	
Heterocodeine		72	65	0.48	0.32	2.40+	1.40	0.016
Dihydromorphinone (Dilaudid)	III-5	84	67	0.17	0.17	0.08	0.88	0.011
Dihydrocodeinone (Dicodid)	III-6	86	47	1.28	0.86	2.56+	4.20	0.08
Dihydrodesoxymorphine-D (Desomorphine)	III-7	104	104	0.08	0.16		0.32	0.012
Tetrahydrodesoxymorphine		221		0.62	1.86	6.20+	14.0	
Methyldihydromorphinone (Metopon)	III-8	25	25	0.07	0.10	0.07	3.0	0.011
Ethyldihydromorphinone		27	22	0.17	0.09	0.17	2.01	0.021
Dihydrohydroxycodeinone (Eucodal)	III-4	426	426	1.34	0.89	0.89+	1.34	0.10

tutes lacking the addiction liability of morphine. About 125 morphine derivatives were prepared and tested for analgesic and other pharmacological properties. Among the new substances developed during the course of this study, dihydrodesoxymorphine D (desomorphine, III-7) and methyldihydromorphinone (metopon, III-8) are of special interest.

According to Eddy (cf. Burger, p. 161) (6), " Pharmacological and clinical studies of metopon have revealed that it is relatively free from nauseating effects and does not produce mental dullness. It affords adequate relief of chronic deep-seated pain by oral administration and has been introduced for analgesia in inoperable terminal neoplastic disease. Tolerance to metopon and addiction develop slowly. Its main disadvantage is the difficulty of its preparation." Desomorphine has an analgesic action approximately nine times as great as that of morphine. It has the further advantage of being almost entirely free from the emetic and other effects of morphine on the gastro-intestinal tract.[3]

Table IV sets forth the result of a comparative study of morphine and codeine and some of its principal semi-synthetic substitutes.

The survey is taken from " Studies on Drug Addiction " (27) and tabulated in the same way as that of Burger (6).

The following notes explain the column headings in the table :

Toxicity (LD50) : Average fatal dose, amount killing 50 per cent or more of animals used, administered subcutaneously to mice.

Convulsant action : The smallest amount with which convulsions were observed during the determination of the average fatal dose in mice.

Analgesia : Amount of substance administered intramuscularly which caused in at least four of the five cats receiving the dose an increase in the pressure required to evoke a response when applied to the terminal portion of the tail.

Exciting effect : Smallest dose with which definite signs of exciting action were seen in at least two of a group of five cats.

Emetic action : Smallest dose with which a cat vomited, or in many instances, when no dose used caused vomiting, the smallest dose with which nausea, or licking, with or without salivation, occurred.

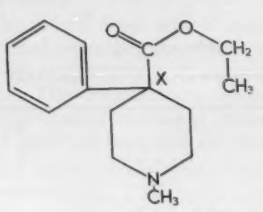
General depression : Smallest dose preventing immediate righting of at least 75 per cent of a group of twenty rats, thirty minutes after intraperitoneal injection.

Respiratory effect : Minimal effective depressant dose as defined by Wright & Barbour : *J. Pharmacol. Exptl. Therap.*, 1937, *61*, p. 422.

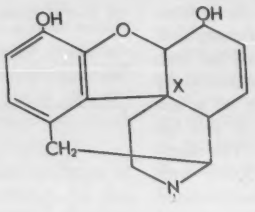
The work of " improving " morphine and the secondary opium alkaloids on the general lines described above is proceeding constantly. For example the drug " pholcodine " (III-9), was recently developed by French investigators (8). Mention must also be made in this connexion of the efforts which have been made to prepare glycosidic derivatives from

[3] See the study entitled " The therapeutic value and the addiction-producing properties of dihydrodesoxymorphine-D (desomorphine) " prepared on request of the World Health Organization by Dr. P. O. Wolff, formerly Chief, Addiction-producing Drugs Section, WHO (Document WHO/APD/54, 14 March 1955—E/CN.7/L.90, 30 March 1955).

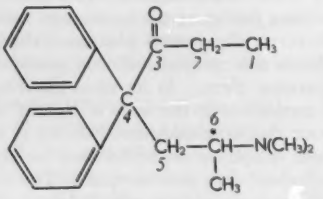
Table V



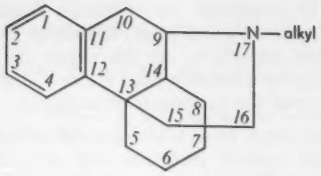
(V-1) — *Pethidine*



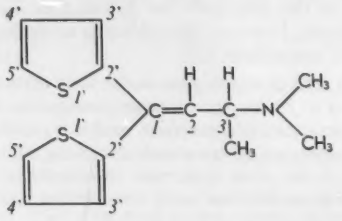
(V-2) — *Morphine*



(V-3) — *Methadone*



(V-4) — *Alkylmorphinan*



(V-5) — *Dimethylthiambutene*

morphine and codeine (17), although the results have not so far been very satisfactory.

7. Synthetic drugs with morphine-like effects

The morphine substitutes in group 2 possess the fundamental structure of morphine. Investigators have sought to attain their objective—i.e., substances having a morphine-like effect but not the addiction liability of morphine—by varying the *peripheral* structure of the morphine molecule. The same is to some extent true with respect to the morphinan group of synthetic morphine substitutes (group 3 d). The situation of the morphine-like drugs of the pethidine-, methadone- and diethienylbutenylamine groups is quite different. These substances may be regarded as the result of *radical* changes in the *central part of the morphine molecule*—about the pharmacophorous nucleus itself : the quaternary carbon atom in position 4 of the piperidine ring (cf. the C atom at the point marked " x " in figures V-1 and V-2).[4]

In contrast to the morphine substitutes of group 2, which are produced with the aid of the opium alkaloids, the corresponding representatives of group 3 are purely artificial products obtained by organic chemical synthesis from generally available chemicals. This also applies to the substances of the morphinan group.

As will be shown, the substances of group 3 are based on the same basic pharmacophorous principle as morphine. They can be prepared by pure organic chemical synthesis, and they are in direct competition with the corresponding natural substances. Only the future will reveal the outcome of this competition, which is dependent on a number of factors.

[4] On the relationship between chemical structure and analgesic action see Braenden, O. J., Eddy, N. B. & Halbach, H. (1955), *Bull. Wld. Hlth. Org. 13*, 937, where features common to the structural formulae of substances with morphine-like analgesic effect are pointed out.

(a) *The Pethidine Group*

If the formula of pethidine (V-1) is compared with that of morphine (V-2) certain points of structural similarity are readily demonstrable. It was, moreover, a comparison of this kind that first led Eisleb & Schaumann and their co-workers in 1937 to suspect that the quaternary carbon atom in the piperidine ring of morphine constituted the molecule's analgiphorous group (6).

The primary purpose of Eisleb & Schaumann's synthesis of pethidine was to produce, not a substitute for morphine, but an antispasmodic of the atropine type. Pharmacological tests showed, however, that the new substance had a pronounced morphine-like effect in addition to its spasmolytic action.

The synthesis of pethidine and the discovery of its analgesic effect opened up a very important new field in synthetic drug manufacture. The new methods of synthesis did not, however, constitute a corresponding advance from the point of view of pharmacology and therapeutics, as the new synthetic morphine substitutes are marred by most of the undesirable side-effects of morphine—especially by its addiction liability. This feature is reported to be especially prominent in ketobemidone (20). On the other hand, some of the new substances exhibit certain *desirable* side-effects which give them specific advantages over morphine and therefore make them clinically superior in special cases. Pethidine itself is the best example of this kind : even though, in a general way, its action is less powerful than that of morphine [5] pethidine is, on account of its marked spasmolytic effect, preferred to morphine in such conditions as biliary and renal colic.

(b) *The Methadone Group*

The laevogyric natural substances usually have a much stronger physiological action than the corresponding dextro-

[5] According to Troxil (1948) (22), the same analgesic effect is achieved with 1 cg methadone, 1.5 cg morphine or 15 cg pethidine.

gyric compounds. This is true of methadone (V-3) also. It is stated (6) that, while the laevogyric compound is about 2.2 times as potent as morphine, the action of the corresponding dextro-isomer is only one-tenth of that of morphine. However, the general pharmacodynamic action of the two substances is so similar that no practical purpose is served by separating them. In its main features, the mode of action of methadone is the same as that of morphine. It also has about the same addiction liability as morphine. The abstinence symptoms on withdrawal are milder and fewer with methadone than with morphine. This feature has been utilized in the treatment of morphine addicts : they are first transferred to an adequate dose of methadone, and then, after about a week, when the morphine in the system has been replaced by methadone, the methadone is withdrawn. Morphinism can be treated in this way with less distress than otherwise. This does not mean, however, that addiction to methadone is less serious than morphinism (22).

Methadone is used as an analgesic in the same way as morphine. It seems to be less apt to cause constipation, nausea, vomiting and pruritus than morphine, and is especially indicated in cases where morphine causes distressing side-effects. As methadone is the most important representative of the methadone group, it does not seem necessary to discuss the others here.

(c) *The Morphinan Group*

The representative of the new synthetic morphine substitutes that is closest to morphine in chemical structure is N-methyl-morphinan (V-4) and its derivatives. The pioneering synthesis in this series was carried out in 1946 by Grewe & Mondon (4). In these compounds there has been a much closer approximation to the structural features of morphine itself than in the two previous groups. Morphinan consists of the fundamental structure of morphine without the ether linkage. It really bears the same chemical relationship to morphine as tropan bears to cocaine and atropine. The synthesis of morphinan was a remarkable advance in several respects : in addition to being the forerunner of the actual synthesis of morphine, it provided the starting-point for a new series of synthetic drugs.

One of these drugs, 3-hydroxy-N-methyl-morphinan, acts about three times as powerfully as morphine on man, and it is three to six times as toxic. It resembles morphine in its action, but its addiction liability is said to be less than that of morphine. It has been used especially in postoperative practice and in incurable cancer (6).

(d) *The Dithienylbutenylamine Group*

The discussion of this group will also be limited to a single representative, *viz.*, 3-dimethylamino-1, 1-di(2'thienyl)-1-butene (cf. V-5), " dimethylthiambutene ".

This substance was synthesized by D. W. Adamson (4) in 1950. As its formula shows, C_1 represents the quaternarily linked carbon atom of the piperidine ring of morphine, marked x in figure V-2. Thus the connexion with the morphine molecule may be anticipated in this case also. The substances of this group likewise have an action strongly resembling that of morphine, but clinical experience with them is as yet relatively scanty.

8. World Trade in the Principal Narcotic Drugs

A survey of the 1953 world trade in opium, morphine and several substances having morphine-like effects is given in table VI (20). As this survey shows, the synthetic morphine substitutes at present account for only a modest proportion of world trade.

Table VI

World trade (imports and exports) in narcotics in 1953

	Kg
1. Raw opium	428,467
2. Morphine	1,532
3. Codeine	15,858
4. Ethylmorphine (dionine)	1,469
5. Diacetylmorphine	42
6. Pethidine	1,878
7. Methadone	88

Summary

1. The therapeutic use of natural drugs is in many cases based on a thousand years' experience of both their effects and their side-effects. In this respect the natural substances have a great advantage over the new synthetic drugs. This rule is valid also in the case of analgesics.

2. By virtue of its traditions and its high reputation with both the medical profession and the public, the poppy is still the most important source of analgetic remedies in the world.

3. Large poppy fields are at present needed for seed production. The by-products of this production (the alkaloid-containing capsules and straw, by application of suitable methods) yield opium alkaloids which at least for the present can compete favourably with synthetic analgesics as far as the cost of manufacture is concerned.

4. The prospects of improving the opium plant in order to obtain varieties with a higher alkaloidal content are greater today than formerly, owing to the development of new methods for effecting mutations.

5. The results obtained by comparative chemical and pharmacological studies of morphine and its derivatives often serve as patterns in the synthesis of the new synthetic morphine substitutes.

6. One of the greatest advantages of the synthetic drug industry lies in its almost unlimited potentialities for making variations of the natural substances and for producing new substances which are not produced by nature.

7. The synthetic drugs industry is not dependent on climatic conditions. It is also affected very little by trade barriers. If the basic raw materials are available, it is the method and the technical equipment that determine the production capacity. Obviously this fact is of great significance in the national economy. It is also clearly a factor which states must take into account in planning for their long-term needs.

8. As far as their margin of therapeutic safety is concerned, the natural drugs are by no means inferior to the synthetic ones. In fact morphine is in this respect superior to all known analgetics. In therapeutic value the natural and synthetic drugs are almost on a par with one another. The extent to which each is used therefore depends largely on such factors as therapeutic traditions, production costs, national interests, trade restrictions, etc.

9. Many of the synthetic morphine substitutes are still so new that their undesirable side-effects are not fully assessable.

In addition, many people are somewhat averse to and distrustful of synthetic drugs, and therefore prefer well-tested natural products.

10. The natural drugs with a morphine-like action which are produced from the poppy plant can readily be manufactured even in countries with an under-developed chemical industry. The corresponding synthetic substances require a relatively highly developed chemical industry equipped with the necessary analytical and biological laboratories.

11. The present study shows that the synthetic drugs at present account for a relatively modest proportion of the annual consumption of the drugs here classified as " drugs with morphine-like effects ".

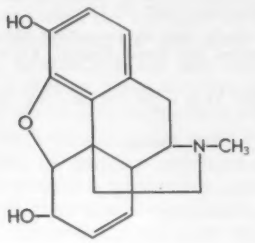
Bibliography

1. BAERHEIM SVENDSEN, A. : *Norges Apotekerforenings Tidsskrift*, 1947, *56*, 523.
2. BAGGESGAARD RASMUSSEN, H. : *Dansk Tidsskrift for Farmaci*, 1954, *28*, 133.
3. BINIECKI, S.; LUDWICKI, H. : *Ann. Pharm. Françaises*, 1953, *11*, 121.
4. BRAENDEN, O. J.; WOLFF, P. O. : *Bulletin of the World Health Organization*, 1954, *10*, 1003.
5. *Bulletin on Narcotics*, 1951, *III* : 2 p. 7.
6. BURGER, A. : *Medicinal Chemistry*, New York, 1951.
7. CASPARIS, P.; BÉCHERT, P. : *Pharm. Acta Helv.*, 1947, *22*, 97, 134.
8. CHABRIER, V.; GIUDICELLI, R.; THUILLIER, J. : *Ann. Pharm. Françaises*, 1950, *8*, 261.
9. DE MEYER, G. : *Les Conventions de l'opium*, Thesis, Zürich, 1950.
10. FRERICHS, G.; ARENDS, G.; ZÖRNIG, H. : *Hagers Handbuch der Pharmaceutischen Praxis*, Berlin, 1949.
11. FULTON, C. C. : *The Opium Poppy and Other Poppies*, U.S. Treasury Department, Bureau of Narcotics, Washington, 1944.
12. Gates, M.; & co-workers : *Journal American Chem. Soc.*, 1950, 72, 228, 4839; 1952, *74*, 1109.
13. GREWE, R.; & co-workers : *Naturwissenschaften*, 1946, *33*, 333; *Chem. Ber.*, 1948, *81*, 279.
14. HENRY, Th. A. : *The Plant Alkaloids*, Philadelphia, 1949.
15. JERMSTAD, A. : *Das Opium*, Vienna and Leipzig, 1921.
16. KARRER, P.; SCHMID, H. : *Helv. Chim. Acta*, 1945, *28*, 722.
17. KÜHNI, E. : *Ueber Kodeinglykoside*, Inaugural lecture, Zürich, 1950.
18. LAUTENSCHLÄGER, C. L. : *50 Jahre Arzneimittelforschung*, 1955, Stuttgart.
19. LEINZINGER, E. : *Pharm. Acta Helv.*, 1947, *22*, 116.
20. *List of the Basic Narcotic Drugs coming under the International Narcotic Treaties*, United Nations, Economic and Social Council, E/CN.7/247, 23. January 1953
21. MANSKE, R. H. F.; HOLMES, H. L. : *The Alkaloids*, 1952, New York, *II*.
22. MÖLLER, K. O. : *Farmakology*, 1952, Copenhagen.
23. MÖLLER, K. O. : *Ugeskrift for Læger*, 1953, *115*, 1683.
24. PERROT, E. : *Journ. Pharm. Belgique*, 1949, *4*, 75.
25. POULSSON, E. : *Lerhbuch der Pharmakologie*, revised by G. Liljestrand, Oslo, 1944.
26. *Report to the Economic and Social Council on Statistics of Narcotics for 1953 and the Work of the Board in 1954*. United Nations, Geneva, 1954.
27. SMALL, L. F.; EDDY, N. B.; MOSETTIG, E.; HIMMELSBACH, C. K. : *Studies on Drug Addiction*, U.S.Treasury Department, Washington, 1938.
28. Generally available reference books, text books, etc.
29. Shaw and Shulman : *Nature*, 1955, *175*, 388.

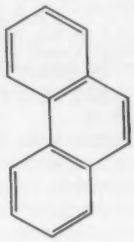
Some New Analgesics and Antispasmodics

By Prof. Dr. Gustav Ehrhart Farbwerke Hoechst AG.

The synthesis of analgesics, particularly of morphine-like compounds, has always been a point of major interest in drug research. For decades, scientists throughout the world have attempted to develop effective analgesics by " re-building " the morphine molecule, considering its constitution a combination of certain " basic skeletons " from which they started their syntheses.



Morphine



Phenanthrene

For years the phenanthrene structure of morphine formed the focus of interest of this work, which, however, was not crowned by success. Strong, effective analgesics were not found in this way.

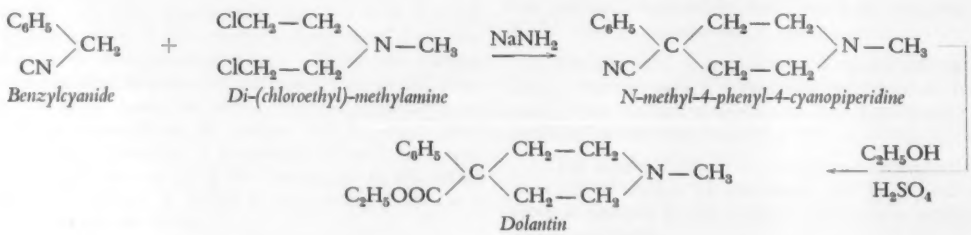
In this article we wish to report on a trend which the pharmaceutical laboratories with which the author is associated have followed for about fifteen years and which led to a series of variously acting synthetic drugs. During the last ten years many interested pharmaceutical-chemical research laboratories throughout the world have joined in the work of further developing these preparations.

The substances concerned are principally compounds with a central quaternary carbon atom — on the one side derivatives of 4-phenyl-piperidine, and on the other those of the diphenylmethane series.

Derivatives of 4-phenylpiperidine

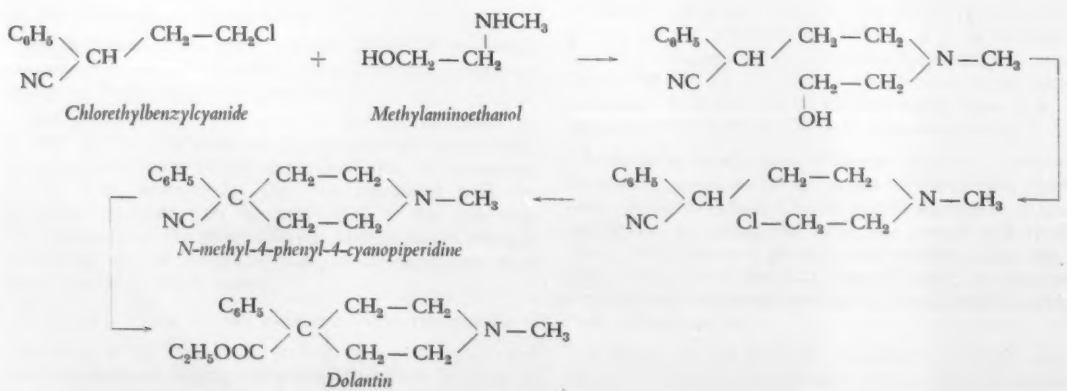
In 1939, O. Eisleb (1) synthesized at Farbwerke Hoechst the ethyl ester of N-methyl-4-phenyl-4-piperidinecarboxylic acid (known by the trade name of Dolantin ®). Its morphine-like effect was discovered by O. Schaumann (2). Outside Germany, this compound is known and marketed under various names, such as Pethidine, Demerol ®, Centralgin, ® Meperidin and others.

Eisleb's synthesis of Dolantin consisted in the condensation of benzyl cyanide with di-(chloroethyl)-methylamine under the influence of sodium amide to N-methyl-4-phenyl-4-cyanopiperidine, subsequent hydrolysis of this compound to the carboxylic acid and esterification to N-methyl-4-phenyl-4-piperidine-carboxylic acid ethyl ester :



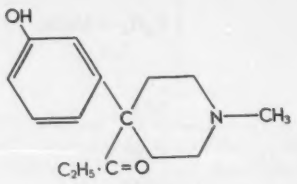
DOLANTIN

A disadvantage of this smooth and simple synthesis is the use of the highly irritating nitrogen mustard gas. In order to avoid this substance we have developed several modifications of this synthesis for the large-scale manufacture of Dolantin. The following scheme represents one of these methods in which the piperidine ring is formed in two stages :



As an analgesic, Dolantin is not as powerful as morphine, but it has the great advantage of affecting the respiratory centre far less than the latter. Besides, it is a good antispasmodic and is successfully used in the treatment of colic pain. It is employed as an analgesic in obstetrics, and Dolantin has lately also been given before anaesthesia. In the modern methods of controlled lowering of blood pressure and artificial induction of hibernation, Dolantin has almost completely ousted morphine.

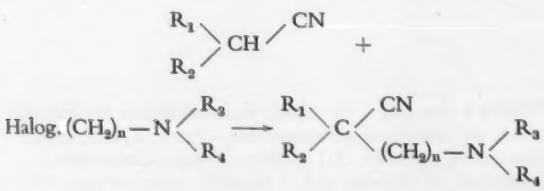
Once the analgesic effect of the 4-phenylpiperidine derivative was recognized, the synthesis of further similar compounds exerted a great attraction for the synthesist and many Dolantin derivatives were produced. We wish to mention only Cliradon®, which, like morphine, has a hydroxy group attached to the phenyl nucleus and a propionyl radical instead of the carbethoxy radical.



Cliradon

Derivatives of Diphenylmethane

The condensation of disubstituted acetoniltriles with basic halogenated compounds represented a further advance in the synthesis of pharmaceutically effective substances with a quaternary central carbon atom. The reaction occurred according to the general scheme



and gave rise to the formation of nitriles substituted by basic radicals (3).

This opened up a wide field of new reactions and numerous new compounds. Even to-day almost all laboratories throughout the world which are interested in these substances are engaged in work for further variations of these compounds and carry out pharmacological and clinical tests with regard to their efficiency. For the resulting basic nitriles must be subjected to a great variety of chemical reactions. We wish to mention only the most important ones :

(A) On treatment with Grignard reagents they are converted into ketones of powerful analgesic action which, in some cases, even surpasses the intensity of morphine.

(B) The reduction of the ketones gives rise to carbinols. Although of no direct pharmalogical importance, esterification of the carbinols restores the analgesic action.

(C) By splitting off the cyanide group under the influence of sodium amide, substituted amines with good antispasmodic and antihistaminic action are obtained.

(D) On partial hydrolysis of the cyanide group, basic acid amides are produced with good antispasmodic properties which are due to the neurotropic group.

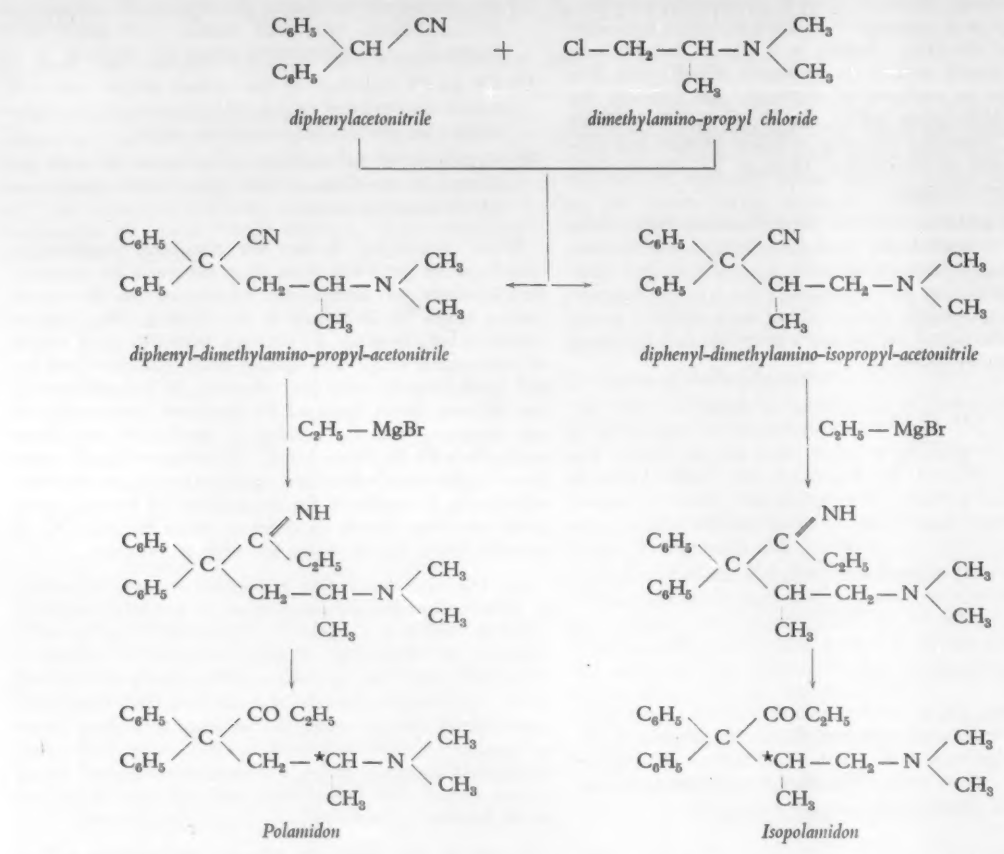
(E) Hydrolysis of the nitril group to carboxylic acids and subsequent esterification yield basic esters which possess an analgesic action.

When considering further the numerous modifications which can be produced from these substances by aromatic, hydroaromatic or heterocyclic substituents on the central carbon atom, by alterations in the aliphatic side chain or various substitutions on the nitrogen atom, the great variety of compounds which have already been synthesized and are still synthesized becomes quite obvious. In consideration of the different effects displayed by these new compounds it is not surprising that the number of synthesized and tested compounds lies far above 1,000. When estimating the number of publications which have appeared on different methods which may be employed for the synthesis of known recognized substances (partly in order to avoid infringement of patents), 500 is by no means too high an estimate.

(A) The most outstanding preparation amongst the ketones is diphenyldimethyl-aminoheptanone, a powerful analgesic, which is known in Germany as Polamidon ® and in other countries as Methadon, Amidon, Ketelgin ®, Adanon ®, Dolophin®, etc. The synthesis of Polamidon is smooth and clear : 3 diphenylacetonitrile is condensed with dimethylamino-propyl chloride under the influence of sodium amide in benzene. A nitrile is formed which is treated with ethylmagnesium bromide, giving a Grignard compound which is then treated with hydrochloric acid and thus hydrolysed to the ketone.

As can be seen from the scheme, condensation with a branched-chain halogen base always yields a mixture of two isomeric nitriles. This surprising isomerization has formed the object of numerous investigations. Nowadays one is inclined to take the view that this transformation is effected by the Na-compound of diphenylacetonitrile. In separating the two isomeric nitriles, their different solubilities are made use of. The analgesic effect of Isopolamidon is slightly less than that of Polamidon. Both Polamidon and Isopolamidon possess an asymmetric carbon atom. In both cases, synthesis gives rise to the inactive racemate of ketones which can be resolved by means of tartaric acid under definite conditions of reaction. In most cases, however, the racemic nitrile is resolved and the optically active nitrile then treated with the Grignard reagent. From the pharmacological point of view it is interesting to observe that practically only the l-form of both Polamidon and Isopolamidon has an analgesic effect, whereas the d-form has hardly any effect. The analgesic action of l-Polamidon is eight times stronger than that of morphine.

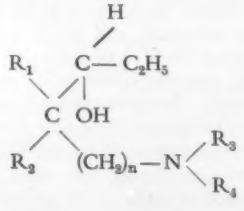
Following this first synthesis of Polamidon, other methods have been employed for the synthesis of this group of substances. We wish to mention the work of Easton, Gardner and Stevens (4), and that of Morrison and Rinderknecht (5). This is not the place to discuss in detail the large number of similarly constituted ketones, but it must be pointed out that in spite of all the numerous variations of the Polamidon



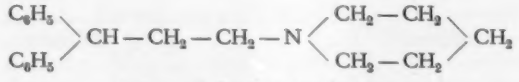
* Asymmetric carbon atom.

molecule no more popular preparation of this group has been found.

(B) As mentioned before, reduction of the ketones gives rise to carbinoles of the type

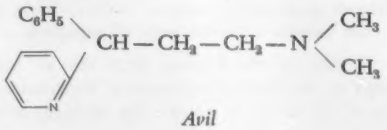


which have no analgesic properties but form powerful analgesics if they are esterified with acid chlorides or anhydrides. Sometimes their action surpasses even that of the ketones. In clinical use, however, they have not proved as valuable as the ketones. By splitting off the CN radical under the influence of sodium amide in an inert solvent (the CN-group is replaced by a hydrogen atom and is used in the formation of sodium cyanamide) — a reaction described already in "Liebig's Annalen" (3) — basic diphenylalkanes are formed which are important antispasmodics. From diphenylpiperidinoethyl-acetonitrile, 1:1 diphenyl-3-piperidinopropane, a constituent of Aspasan and a valuable musculotropic antispasmodic is thus obtained. Its action is about ten to twelve times greater than that of papaverine, a naturally occurring alkaloid.



1 : 1 — *diphenyl-3-piperidinopropane*

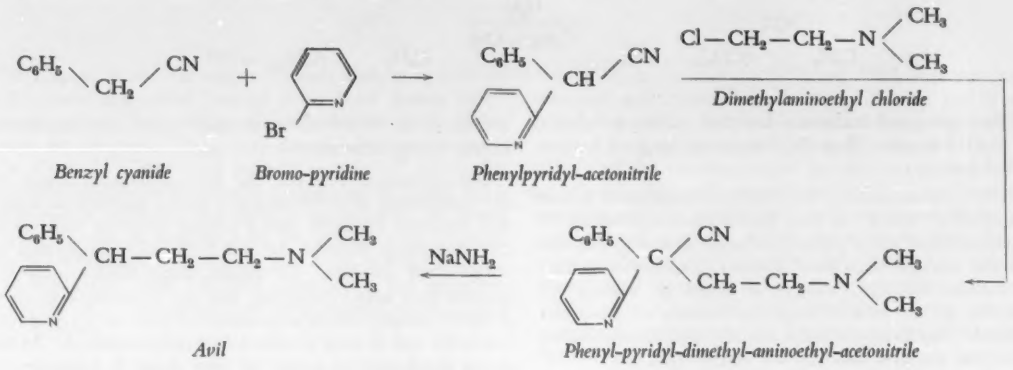
The introduction of heterocyclic ring systems instead of the phenyl radical constituted an important advance. In this way the antihistamine Avil ® (known in the U.S.A. as Trimeton ®) was produced.



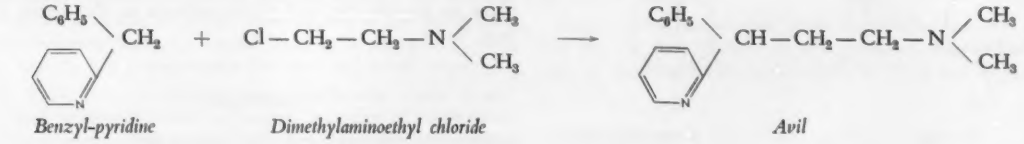
Avil

(C) The synthesis of Avil is generally accomplished by one of the following two methods :

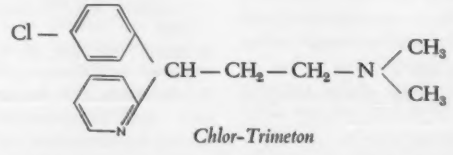
(1) 2-Bromopyridin is treated with benzyl cyanide in the presence of sodium amide to give phenyl-pyridyl (2) -acetonitrile. This is condensed in known manner with dimethylaminoethylchloride under the influence of sodium amide and finally the cyanide group split off as described above.



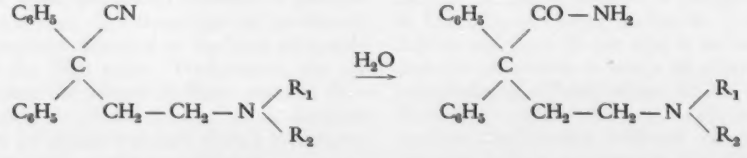
(2) The second method was developed by Sperber *et al* (6) and the research laboratories at Hoechst, independently of each other. It starts with benzylpyridine, which is directly condensed with dimethylaminoethyl chloride to 1-phenyl-1-pyridyl-3-dimethylaminopropane.



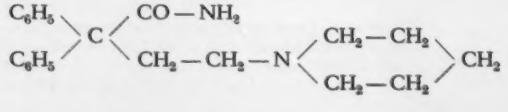
Numerous antihistamines of similar constitution were also synthesized and valuable drugs obtained. A particularly strong effect is exercised by the p-chloro-compound which is marketed under the trade name of Chlor-Trimeton.



(D) Partial hydrolysis of the diphenylacetonitriles carrying basic substituents is accomplished with sulphuric acid or alcoholic potash and produces basic diphenylacetamides.

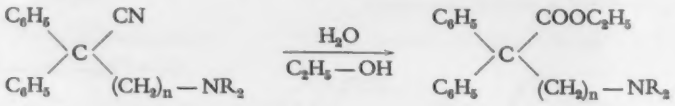


Their analgesic effect is low; but as neurotropic antispasmodics they are very valuable. For instance, the action of diphenylpiperidinoethylacetamide, a constituent of the antispasmodic Efosin ®,



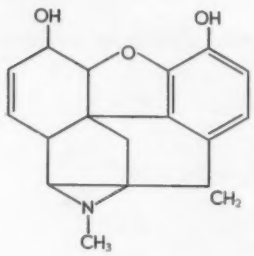
surpasses even that of atropine.

(E) Finally, we wish to mention the group of esters which can be produced by hydrolysis of the above-mentioned nitriles with sulphuric acid, followed by esterification, in one single operation.

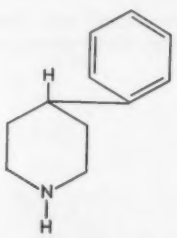


The esters are good analgesics, but their action is inferior to that of the ketones. They are therefore of no great interest in clinical use.

We have now described two types of compounds whose pharmacological action is very similar—i.e., derivatives of 4-phenylpiperidine and diphenylmethane. It is only natural to look for similarities in their chemical constitution which might account for this analogy. In order to attempt an explanation, we are now writing the formula of morphine in a different way from the usual one, showing a constitution published for the first time by O. Schaumann (7) :



Morphine



4-phenylpiperidine

This formula emphasizes and justifies the conception of morphine as a 4-phenylpiperidine derivative, and, furthermore, we recognize the central quaternary carbon atom mentioned before as common to all the compounds described. We have thus found a parallel between Dolantin (or Cliradon) and diphenylmethane on the one side and morphine on the other.

But we should not forget that all this is more or less an assumption, and that the explanation of the pharmacological action of the described compounds is only an attempt and by no means definitive.

The connexion between the pharmacological action and the constitution of a compound is an old problem in medical and chemical research; but a critical observer must notice that not much progress has yet been made in solving this complicated question. Of course, some fundamental connexions have been recognized, and the experienced synthesist is able to foretell the possible action of a chemical compound, but in the end all these prophecies are only empirical. As long as the mechanism of action of most drugs is unknown and only assumed, we cannot claim to know the actual connexion between constitution and effect. Even today, we might well obtain absolutely surprising and unexpected results when testing a new compound for its pharmacological effect — a fact proving our ignorance in this matter, but on the other hand, being a continuous incentive and encouragement to the chemist and pharmacologist in the search for new drugs.

Literature

1. Eisleb, O. : *Ber. dtsch. chem. Ges.*, 1941, *74*, 1441.
2. Schaumann, O. : *Arch. f. exp. Path. u. Pharm.*, 1940, *196*, 109.
3. Bockmühl, M.; Ehrhart, G.; Schaumann, O. *Liebigs Annalen*,: 1948, *561*, 52.
4. Easton, N. R.; Gardner, J. H.; Stevens, J. R. : *Journal Am. Chem. Soc.*, 1947, *69*, 2941.
5. Morrison, A. L.; Rinderknecht, H. : *J. Chem. Soc.* (London), 1950, 1478.
6. Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M.; Fricano, R. : *Journal Am. Chem. Soc.*, 1951, *73*, 5752.
7. Schaumann, O. : *Pharmazie*, 1949, *4*, 364.

OFFICIAL

Legal Trade in Narcotics in 1954

The Report of the Permanent Central Opium Board [1] to the Economic and Social Council on its work during 1955 [2] is on the agenda both of the eleventh session of the Commission on Narcotic Drugs and the twenty-second session of the Council. This report presents an over-all picture for 1954 of the legal trade in narcotics throughout the world at it is shown by the analysis of the statistics submitted to the Board by governments, in pursuance of the international Conventions of 19 February 1925 and 13 July 1931, and the Protocol of 19 November 1948. A brief summary of the main features included in the report of the Permanent Central Opium Board follows.

Trends in the licit movement of narcotic drugs

Raw Materials

(a) *Opium*

In 1952 and 1953, the licit production of opium had exceeded requirements and large stocks were piling up, mainly in the producing countries, so that at the end of 1953 the amount of opium available in those countries and in the morphine-manufacturing countries would have been enough to meet the world's licit requirements for two and a half years.

In 1954, licit production was considerably reduced and demand increased, so that it became necessary to draw upon stocks to meet requirements. At the end of the year, stocks were sufficient to meet the world's requirements for about two years.

The Board continues to feel some concern with regard to available supplies of opium, by reason of the fact that governments are not invariably able to ensure that all opium harvested is surrendered to them and their production figures accordingly represent only the quantities bought from producers by State monopolies. Positive evidence that the Board's apprehensions in this respect are well founded has been provided this year by the disclosures in Iran. The amount of opium delivered to the State monopoly by Iranian producers during the last ten years, which was said to represent total production, averaged 140 tons a year from 1945 to 1954. According to statements made by the Health Minister of Iran at a press conference in Teheran on 4 August 1955, however, the actual production amounts to between 700 and 1,200 tons a year. It follows that the production in excess of the quantities delivered to the State monopoly must have entered the illicit traffic. Furthermore, the circumstances surrounding the seizures of illicit opium in different parts of the world clearly indicate that similar diversion is occurring in other producing countries, though it is impossible to estimate the total quantities so diverted.

The total world declared production fell from 1,295 tons in 1953 to 773 tons in 1954 — that is, by 40 per cent.

In 1954, in contrast to 1952 and 1953, licit requirements increased and exceeded production. The increase is due to higher demand by morphine-manufacturing countries. "Quasi-medical" requirements are falling steadily, as a result particularly of the measures taken by the Government of India to abolish this use entirely by 1959. *Licit* non-medical requirements are now very small compared with medical requirements, whereas before the 1939-45 war they were substantially larger. In 1954, two countries supplied the Board with figures of their licit non-medical consumption. They were Cambodia and Thailand, where consumption amounted, respectively, to 78 kg. and 16,448 kg; in the latter country the opium used for this purpose seems to have come entirely from confiscations in the illicit traffic. India supplies only aggregate figures for opium smoked and opium used for quasi-medical purposes. In 1954, the total figure was 83,505 kg.; by far the greatest part was used for quasi-medical purposes.

(b) *Poppy Straw*

Poppy straw has assumed great importance as a raw material for the manufacture of morphine : it supplied 26 per cent of world morphine production in 1953, and 22 per cent in 1954.

(c) *Coca Leaves*

Total world production of coca leaves in 1954 amounted approximately to 13,113 tons. This total is shared very unequally among the four producing countries. Peru heads the list with 9,907 tons, followed by Bolivia with 3,000 tons, Colombia with 180 tons and Indonesia with 26 tons. Cultivation of the coca shrub, which had been started again in the Chinese province of Taiwan (Formosa), yielded an initial crop of 200 kg. in 1953, but no harvest took place in 1954. In Peru the amount harvested rose from 9,502 tons in 1953 to 9,907 tons in 1954.

The use of coca leaves for medical purposes—namely, for the licit manufacture of cocaine—absorbed only a fraction of the output (less than 700 tons out of the world total of 13,113 tons in 1954). The balance, over 12,000 tons, was consumed for non-medical purposes—that is to say, was chewed by certain indigenous peoples of South America. In Colombia the entire production is used in this way; in Bolivia and Peru 90 per cent is so used. The balance of Bolivia's production is nearly all exported to Argentina, a non-producing country where the leaf-chewing habit exists. Peru, on the other hand, exports the rest of its crop to the cocaine-manufacturing countries. In Indonesia, where the chewing habit is non-existent, the whole crop is exported for the purposes of cocaine extraction.

(d) *Cannabis (Indian hemp) Preparations for Medical and Quasi-medical Use*

In 1953, according to the latest statistics reaching the Board, 1,300 kg. of these preparations were used in the world—more than half in India and Pakistan, and the rest in some twenty

[1] Document E/OB/11, November 1955.

[2] For the report of the Permanent Central Opium Board on its work in 1951, see *Bulletin on Narcotics*, Vol. IV, No. 2; for the report on 1952, see idem, Vol. V, No. 1; for the report on 1953, see idem, Vol. VI, No. 1; for the report on 1954, see idem, Vol. VII, No. 1.

other countries. The information which the Board possesses for 1954 indicates that the use of cannabis preparations has fallen to 900 kg. It ceased altogether in France and Chile, and apparently also in Pakistan, and fell by half or even more in the United Kingdom, the Union of South Africa, Australia, New Zealand, Ireland, Sweden and Norway.

Manufactured Drugs

(a) *Morphine*

After declining in 1953, world manufacture resumed its upward movement in 1954, rising from 74 to 84 tons. Both the rate of increase and the figure of 84 tons are the highest on record.

The rise in world manufacture is due to the continually increasing requirements for codeine, the production of which accounts every year for 80-90 per cent of the morphine manufactured. In 1954, the quantity of morphine converted into ethylmorphine, pholcodine and hydromorphone also increased, and it now represents 8 per cent of total morphine production. It follows that the amount of morphine not converted into other drugs now represents only a small fraction of total production, being less than 5 per cent during the last two years, or an absolute figure of 3 tons. World consumption of morphine, on the other hand, during the year was 5 tons, and the deficit had to be made good by drawing upon stocks.

Morphine is now much less widely used in medical practice than before the war and is presumably being replaced by other drugs, either opiates or synthetics with comparable effects.

(b) *Diacetylmorphine*

Three countries continued to manufacture diacetylmorphine in 1954 : the United Kingdom (120 kg.), Belgium (8 kg.) and Portugal (4 kg.), making a total of 132 kg., or 26 kg. less than in 1953.

World consumption fell from 206 kg. in 1953 to 158 kg. in 1954. Since 1951, production has been even lower, and this has led to a gradual reduction of stocks.

(c) *Codeine*

Consumption of no other drug has increased in such proportions as that of codeine. During the twenty years for which the Board possesses statistics, consumption of codeine has increased fourfold, showing a steady rise from 18 tons in 1935 to 68 tons in 1954, the maximum so far recorded. This trend may be explained by the growth of population, the expansion of medical services and the more varied use which medical practice has found for this drug.

(d) *Cocaine*

World production rose from 1,995 kg. in 1953 to 2,428 kg. in 1954. This increase of over 20 per cent is due to growing demand in the following countries : USSR, China (Mainland), Romania, Indonesia and Poland. Exports to these countries, which were 216 kg. in 1953, rose to 670 kg. in 1954. The biggest rise is in the figures for the USSR (from 90 kg. to 450 kg.). So far as can be seen from the statistics, the imports were intended partly for current consumption and partly for the replenishment of stocks. The supplying countries (Federal Republic of Germany, United Kingdom, Netherlands and France) accordingly raised their production from 1,021 kg. to 1,429 kg.

(e) *Synthetic Narcotic Drugs*

(1) Pethidine

World consumption has increased as follows, since 1951, the first year for which the Board has more or less full information :

1951	1952	1953	1954
	(Tons)		
8.9	10.3	10.7	11.4

The Board is engaged in a study of the pattern of consumption of pethidine and its relationship to that of morphine.

(2) Methadone

World consumption of methadone, which was 489 kg. in 1953, rose to 553 kg. in 1954. During the same period, production increased from 395 to 609 kg. The production deficit observed in 1953 was thus partially offset in 1954.

(3) Ketobemidone

Up to 1953 this drug was manufactured in Switzerland and Denmark. In 1954, Switzerland suspended its manufacture, and as a result world production fell from 110 kg. in 1953 to 24 kg. in 1954.

World consumption of ketobemidone totalled 64 kg. in 1954, and only in ten countries—Argentina, Belgium, Denmark, Finland, Federal Republic of Germany, Italy, Norway, Portugal, Sweden and Switzerland—did it amount to 1 kg. or more.

New Narcotic Drugs

The Board states that since the publication of its last report [3] the following narcotic drugs, together with their salts, have been placed under international control :

(*a*) Under article 11 of the 1931 Convention :

6-methyldihydromorphine,
Dihydrohydroxymorphinone,
Myristyl ester of benzylmorphine;

(*b*) Under the 1948 Protocol :

4,4-diphenyl-6-dimethylamino-3-hexanone,
β-6-dimethylamino-4,4-diphenyl-3-heptanol (beta methadol),
4,4-diphenyl-6-piperidino-3-heptanone,
Isopropyl and other esters of 1-methyl-4-phenylpiperidine-4-carboxylic acid.

These were subjected to the regime applying to the drugs specified in article 1, paragraph 2, Group I, of the 1931 Convention, except for the myristyl ester of benzylmorphine; this drug is only provisionally subjected to that regime, and its definitive regime will be determined later.[4]

Conclusions

In 1954, production of raw opium was reduced and demand increased slightly, thereby bringing the stocks down to about two years' requirements.

Consumption for medical and scientific purposes of most of the " manufactured " drugs continued to rise in 1954 as in previous years, the rise being probably attributable to the growth of population and improvement in

[3] See *Bulletin on Narcotics*, Vol. VII, No. 1.
[4] See *infra*, page 37.

standards of living. In itself, therefore, the fact affords no reason for disquiet, and indeed consumption may be expected to rise further as health services continue to expand. At the same time a responsibility rests on governments to ensure that proper care is exercised in prescribing these substances.

It is essential also that as soon as any new drug, synthetic or other, is authoritatively stated to possess addiction-producing properties the medical profession should be fully alerted to the dangers attaching to its use, and this need is engaging the attention of the Commission on Narcotic Drugs and of the World Health Organization.[5]

The quantities of opium consumed both for licit and illicit non-medical purposes and for quasi-medical purposes, and the quantities of coca leaves for chewing, are overwhelmingly greater than the quantities required for strictly medical and scientific ends.

Opium is clearly still the main element in the illicit consumption of narcotics : there are millions of opium addicts, particularly in Asia, and the illicit traffic in opium also supplies the clandestine laboratories which manufacture almost all the morphine and diacetylmorphine used by drug addicts.

Second only to opium in this respect are cannabis resin (hashish, charas, chira) and cannabis leaves and tops (ganja, bhang, dagga, kif, takrouri, marihuana, maconha), the abuse of which is practised by millions of addicts all over the world.

[5] See *infra*, page 37.

The chewing of coca leaves, a habit which again is shared by millions of people, is confined to certain countries of South America. The amounts thus consumed are nearly twenty times as great as those used for the licit manufacture of cocaine. In 1954, a long-standing controversy was brought to an end when it was agreed between the governments concerned, the World Health Organization and the Commission on Narcotic Drugs that this habit constitutes a form of drug addiction, even though it does not possess all the characteristics of addiction, and that it should be suppressed.

While the gravity of the problem of addiction to morphine and its derivatives, particularly diacetylmorphine, and to cocaine is not in any degree minimized by the comparison, it is nevertheless true that the addicts to these drugs, who are to be found in nearly all parts of the world, are infinitely fewer than the habitual consumers of either opium, cannabis or coca leaves; and, to judge by the reports on illicit traffic, persons addicted to " synthetic " narcotics must be fewer still.

In all countries, whether they be producers of raw materials, manufacturers, or merely consumers of narcotic drugs, effective national control is the primary pre-requisite for satisfactory fulfilment of the International Conventions. But each country has its own special problems, and these can be solved only with the continuing support of public opinion, on which the success of all efforts against the various forms of drug addiction ultimately depends.

Estimated World Requirements of Narcotic Drugs in 1956

The International Convention of 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs introduced the obligatory estimate system to carry out the principle of limiting the manufacture and trade of narcotic drugs to medical and scientific purposes. Each country and territory is to furnish, annually, advance estimates of the narcotic drugs needed for these purposes. These estimates are binding and determine the maximum amounts to be manufactured or imported in any given year. The estimates are examined by the Drug Supervisory Body, an organ composed of four experts sitting in their personal capacity — i.e., they are not governement representatives. The Supervisory Body may require further information from governments on their estimates and may, *with their consent*, change the estimates. It publishes an annual statement of estimates for each country or territory and, if considered necessary, an account of the explanations given by gouvernments or required from them.

It was felt that it would be of interest to the readers of the *Bulletin* to know, for the most important narcotic drugs, what the world total estimates had been from 1950 to 1956, together with the actual figures of production for these drugs from 1950 to 1954 (the last year for which statistics have been published by the Board). The figures on estimates have been taken from the documents *Estimated World Requirements of Narcotic Drugs in 1956* (E/DSB/13) and the fourth supplement to the corresponding document for 1955 (E/DSB/12/Add.4), published by the Supervisory Body.

It will be noticed that the estimates exceed the actual production by amounts ranging from 20 per cent up to more than 70 per cent : the Supervisory Body states in that connexion that several countries submit estimates which can be up to four times greater than their annual requirements, because they fear to get insufficient supply otherwise (although the Convention allows governments to submit supplementary estimates or to amend any inadequate estimates). From 1953 onward, the Supervisory Body has been trying to correct this state of affairs, with some success, by drawing the attention of governments to the uselessness of unduly large estimates.

Among the interesting facts shown by these estimates, two can be emphasized : first, the estimated requirements of diacetylmorphine have fallen steadily since 1948, as a result of the efforts made by international bodies to persuade govern-

ments to prohibit the use of this drug. Indeed, the actual production has fallen even more markedly, owing to the fact that certain governments (Canada, Argentina, Finland, for example) which have decided to abandon the use of diacetylmorphine are using up their stocks. Thus, the estimated requirements and the production of this drug fell respectively from 972 kg. and 839 kg. in 1948 to 338 kg. and 132 kg. in 1954. The world total of the estimates further decreased to 259 kg. for 1955 and 151 kg. for 1956; the latter figure may of course be modified during the year by revised or supplementary estimates.

Secondly, the number of synthetic narcotic drugs is increasing from year to year, and an increasing number of countries and territories are using them. The apparent increase in the total estimated requirements of synthetic narcotic drugs other than pethidine does not mean that consumption of these drugs is rising at a uniform rate in the countries which used them first. It must also be noted that many of these drugs are still the subject of clinical experiment. In short, it does not seem always to be easy for national authorities to estimate precisely their country's requirements of newly discovered drugs.

The Supervisory Body also notes that total estimated requirements of ketobemidone have diminished considerably between 1953 and 1955. This is no doubt a sign that governments have taken heed of the resolution adopted on 12 July 1954 by the Economic and Social Council of the United Nations.[6] From 278 kg., the record figure of 1953, the total estimates fell to 175 kg. for 1955 and 72 kg. for 1956; this total will be modified during the year 1956 by supplementary estimates. Twenty-nine countries supplied estimates of ketobemidone for 1953; this number has fallen to twenty-four for 1956.

[6] Resolution 548 H II (XVII).

World Total Estimates from 1950 to 1956 and Production from 1950 to 1954

(In kilogrammes)

Drug	1950		1951		1952		1953		1954		1955	1956[a]
	Estimate	Production	Estimate	Production	Estimate	Production	Estimate	Production	Estimate	Production	Estimate	Estimate
Morphine[b]	96,985	65,749★	100,327	72,566★	100,460	78,111★	92,583	73,817★	103,235	83,501★	105,589	93,452
Diacetylmorphine	843	450★	730	381★	464	120	295	158	338	132	259	151
Thebaine	3,113	1,133★	3,365	1,970★	3,281	1,729	2,859	2,315	3,219	2,040	3,228	2,127
Codeine	90,597	57,708★	89,773	66,490★	86,900	65,070★	83,476	66,444★	94,940	75,395★	99,065	80,172
Ethylmorphine	8,675	3,626★	10,198	6,178★	9,041	5,432★	8,824	5,121★	9,730	5,191★	9,667	6,800
Cocaine	5,834	1,288★	6,174	1,522	4,621	2,171	4,390	1,995	4,822	2,428	3,797	2,889
Pethidine	8,198	7,423★	10,919	12,154★	22,774	11,612★	20,184	10,320	19,947	12,555	17,927	13,965
Methadone	1,694	510★	1,794	521★	908	381★	929	395★	792	609	900	751

[a] The 1956 estimates will be modified during the year by revised or supplementary estimates.
[b] It should be pointed out that from 80 to 90 per cent of the morphine is to be converted into codeine (a small percentage into other drugs).
★ Figures marked with an asterisk are incomplete: most but not all the countries have furnished statistics.

World Health Organization : Expert Committee on Drugs liable to Produce Addiction

Sixth Report [1]

The Expert Committee on Drugs liable to Produce Addiction of the World Health Organization held its sixth session in Geneva from 24 to 29 October 1955 and made a report, which was adopted by the Executive Board of the World Health Organization at its seventeenth session, held in Geneva from 17 January to 2 February 1956 (resolution EB17.R3, *Official Records of the World Health Organization*, 1956, *68*, 2). The main features are as follows :

Report on the Tenth Session of the Commission on Narcotic Drugs of the United Nations Economic and Social Council

The Committee took particular note of the discussion of synthetic substances in the report on the tenth session of the Commission on Narcotic Drugs to the United Nations Economic and Social Council,[2] and of resolution No. 588 (XX) D relating thereto, which was adopted at the twentieth session of the Council.[3] The Committee was of the opinion that any narcotic substance, whether synthetic or derived from a natural alkaloid, must be considered individually, and that for the purposes of control no distinction should be made between the group of natural alkaloids and their derivatives on the one hand and the group of synthetic substances on the other. Further reference to this point is made under the heading " Morphine and its derivatives ".

The Committee was pleased to note the decision of the Commission on Narcotic Drugs to recommend that governments should limit their imports of coca leaf and crude cocaine in a manner analogous to that applicable to opium under the Protocol of 1953, and the decision to place cannabis drugs together with diacetylmorphine (heroin) and ketobemidone in the list of prohibited drugs (Schedule IV) to be included in the proposed Single Convention on Narcotic Drugs.

The Committee discussed the seriousness of the placing of drugs in any prohibiting list and expressed the view that it would welcome an opportunity to consider and give advice on substances which might be placed in that schedule.

The Committee was pleased to note further that in the provisions of the Single Convention the World Health Organization, as well as governments, should have initiative in notification of new substances and of changes in the position of substances under control regimes.

Resolutions of the United Nations Economic and Social Council

The Committee was pleased to note in resolution No. 588 (XX) E [4] on abuse of drugs (drug addiction), adopted by the United Nations Economic and Social Council, the recommendations with respect to the continuing effort to collect statistics on the incidence of addiction throughout the world, and with respect to initiation of a study of the best methods for the treatment of addicts.

The Committee took particular note of, and concurred in, the view expressed by the Commission on Narcotic Drugs that in the treatment of drug addiction methods of ambulatory treatment (including the so-called clinic method) are not advisable.

Morphine and its Derivatives

Situation regarding Diacetylmorphine (Heroin)

The Committee noted with satisfaction the resolution of the Commission on Narcotic Drugs of the United Nations Economic and Social Council urging all governments which have not heretofore done so to prohibit the use and manufacture of, and trade in, diacetylmorphine.[5]

It was reported to the Committee that, of the 20 States which have supplied estimates for diacetylmorphine for 1956, only 4 are not prepared to suppress the use of the drug; several of the others have announced that they will discontinue its use when present stocks are exhausted. It was emphasized that in general the estimates are significantly smaller than in former years and that over-all licit production has shrunk from 839 kg. in 1948 to 132 kg. in 1954. The Committee concluded from this information that more and more physicians throughout the world are finding it possible to substitute less dangerous drugs for diacetylmorphine, in accordance with the Committee's repeatedly expressed view on the replaceability of this dangerous addicting agent.

The small number of countries still persisting in the use of diacetylmorphine, the reduction in estimates for the next year, and the marked decrease in production of the drug reflect very gratifying progress in the campaign against diacetylmorphine.

Reconsideration of Certain Sections of the Fifth Report of the Committee on Request of the Executive Board at its Fifteenth Session [6]

It is now almost universally recognized that diacetylmorphine is a dangerously addicting drug. Such was not always the case. Diacetylmorphine was introduced into medicine

[1] *World Health Organization : Technical Report Series*, No. 102.

[2] United Nations, Economic and Social Council, Commission on Narcotic Drugs : Report . . . on the tenth session . . . 18 April to 12 May 1955 (document E/2768 - E/CN. 7/303).

[3] United Nations, Economic and Social Council, *Official Records, Twentieth Session, 5 July-5 August 1955*. Supplement No. 1. Resolutions (document E/2795).

[4] See footnote 3.

[5] See footnote 2.

[6] See *Bulletin*, Vol. VII, No. 2.

little more than fifty years ago as a non-addicting substitute for morphine, and this impression of relative safety was corrected only by accumulated clinical experience.

Pethidine also was introduced with the claim in some quarters of relative safety with respect to addiction liability, and again clinical experience is demonstrating the incorrectness of this claim. The Committee again concluded that pethidine is comparable to morphine in addiction liability; neither pethidine nor morphine is comparable to diacetylmorphine in this respect. The Committee was of the opinion that the rising trend in pethidine addiction [7] can be combated only by recognition of the danger and by as much care in the use of the drug as with morphine.[8]

The Committee wished to emphasize in this connexion its view that synthetic analgesic drugs differ from one another in addiction liability just as do drugs derived from natural substances such as opium; that members of each class must be considered individually with respect to inherent risk and therapeutic advantage; and that the risk of addiction through the use of synthetic drugs is neither greater nor less than the risk encountered through the use of morphine, related opium alkaloids, or substances derived therefrom.

The Committee concluded that morphine, related substances, and synthetic drugs are equally useful for medical needs, and that there is a wide range of potency available among members of each group.

Synthetic Substances with Morphine-like Effect

Synthetic Substances of Morphinan Type

(—)-3-Hydroxy-N-allylmorphinan, also designated l-*3-hydroxy-N-allylmorphinan (levallorphan)* [9]

Referring to the notifications of the Government of Switzerland and of the Government of the United States of America, the Committee reviewed the evidence on levallorphan and found that, like nalorphine, when administered alone it produced dysphoria rather than euphoria and that it had not caused the appearance of tolerance or physical dependence. It would not relieve the abstinence syndrome or sustain a morphine addiction, but would precipitate abstinence phenomena if physical dependence on morphine or a morphine-like drug had been established.

The Committee also considered the conversion of levallorphan to levorphan. Such conversion, although possible, is so difficult that it is considered to be impracticable and to constitute no risk to public health.

The Committee was of the opinion that levallorphan cannot be considered either to be an addiction-producing drug or to be capable of conversion into an addiction-producing drug for the purposes of the 1931 Convention.

(—)-3-Methoxy-N-allylmorphinan

(—)-3-Acetoxy-N-allylmorphinan

Referring to the notification of the Governement of Switzerland, the Committee concluded that the position of these substances is analogous to that of levallorphan and that they cannot be considered either to be addiction-producing drugs or to be capable of conversion into addiction-producing drugs for the purposes of the 1931 Convention.

(—)-3-Hydroxy-N-propargylmorphinan

Referring to the notification of the Government of Switzerland, the Committee decided to reserve judgment with respect to the addiction liability of this substance until information is available on the results of its repeated administration.

3-Hydroxy-N-phenethylmorphinan

Referring to the notification of the Government of the United States of America, the Committee was of the opinion that 3-hydroxy-N-phenethylmorphinan, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered an addiction-producing drug comparable to morphine, and that 3-hydroxy-N-phenethylmorphinan and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I.

The Committee noted further that the very great potency of 3-hydroxy-N-phenethylmorphinan with respect to the production of morphine-like effects and to the suppression of morphine abstinence phenomena indicates that the substance possesses particularly dangerous addiction-producing properties. It emphasized the desirability of avoiding the manufacture, import, and export of these substances, unless a definite therapeutic advantage can be shown.

Synthetic Substances of Methadone Type

4-Morpholino-2,2-diphenyl ethyl butyrate, designated also ethyl-2,2-diphenyl-4-morpholinobutyrate

Referring to the notifications of the Government of Italy and of the Governement of the United States of America, the Committee was of the opinion that 4-morpholino-2,2-diphenyl ethyl butyrate, because it produces marked and prolonged morphine-like effects comparable to those of other addiction-producing substances related to methadone, must be considered an addiction-producing drug comparable to morphine and that 4-morpholino-2,2-diphenyl ethyl butyrate and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I.

4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane

Referring to the notification of the Governement of the United States of America, the Committee was of the opinion that 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane, because it (1) will only partially suppress the abstinence phenomena of a known morphine addiction, and (2) will in part sustain a morphine addiction, must be considered as having no greater addiction liability than codeine, and that 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane and its salts are assimilable to the drugs mentioned in Group II of the 1931 Convention.

4,4-Diphenyl-6-piperidino-3-hexanone

The Committee's attention was drawn to the above substance, which has been marketed in Hungary under the name of Hexalgon and has been mentioned in the estimates for that country.

The Committee noted that in previous reports 4,4-diphenyl-6-dimethylamino-3-heptanone (methadone) and 4,4-diphe-

[7] See *Wld Hlth Org. techn. Rep. Ser.*, 1955, *95*, 13. During the period covered in the Lexington report, the total number of addicts treated at the Public Health Service Hospital, Lexington, Kentucky, USA, irrespective of the drug of addiction, was 12 682.

[8] See *Wld Hlth Org., techn. Rep. Ser.*, 1955, *95*, 10 (section 7.3.2).

[9] Proposed international non-proprietary name.

nyl-6-piperidino-3-heptanone were shown to be closely related chemically and to have similar pharmacological properties and similar addiction liability. It is now apparent that 4,4-diphenyl-6-dimethylamino-3-hexanone and 4,4-diphenyl-6-piperidino-3-hexanone are likewise chemically and pharmacologically similar. 4,4-Diphenyl-6-dimethylamino-3-hexanone has been shown to have addiction liability. Because of these analogies, the Committee concluded that 4,4 diphenyl-6-piperidino-3-hexanone must be considered as also having addiction liability.

Synthetic Substances of Dithienylbutenylamine Type

3-Diethylamino-1,1-di-(2'-thienyl)-1-butene (diethylthiambutene[10])

Referring to the notification of the Governement of the United Kingdom of Great Britan and Northern Ireland, the Committee was of the opinion that 3-diethylamino-1,1-di-(2'-thienyl)-1-butene, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered an addiction-producing substance comparable to morphine, and that 3-diethylamino-1,1-di-(2'-thienyl)-1-butene and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I.

Synthetic Substances of Pethidine Type

1-[2-(p-Aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester, designated also 1-[2-(p-aminophenyl)-ethyl]-4-carbethoxy-4-phenylpiperidine

1-(2-Hydroxy-2-phenyl-ethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester, designated also 4-carbethoxy-1-(2-hydroxy-2-phenyl-ethyl)-4-phenylpiperidine

The Committee considered the notification of the Government of the United States of America with regard to these substances and noted particularly that, whereas the analgesic effectiveness of both compounds experimentally is about three times that of pethidine, the dose of 1-[2-(*p*-aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester to produce morphine-like effects is significantly greater than the dose of morphine for a similar effect. Recognizing that the information available at the present time is of a preliminary nature, the Committee decided to defer its opinion with respect to the addiction liability of both compounds.

Synthetic Substances of Hexamethyleneimine Type

1,-3Dimethyl-4-phenyl-4-propionoxyhexamethyleneimine

Referring to the notification of the Government of the United States of America, the Committee was of the opinion that 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered an addiction-producing drug comparable to morphine, and that 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I.

1-Methyl-4-phenylhexamethyleneimine-4-carboxylic acid ester, designated also 4-carbethoxy-1-methyl-4-phenylhexamethyleneimine

1,3-Dimethyl-4-phenylhexamethyleneimine-4-carboxylic acid ethyl ester, designated also 4-carbethoxy-1,3-dimethyl-4-phenylhexamethyleneimine

1,2-Dimethyl-4-phenylhexamethyleneimine-4-carboxylic acid methyl ester, designated also 4-carbmethoxy-1,2-dimethyl-4-phenylhexamethyleneimine

Considering the notification of the Government of the United States of America with respect to these three substances, the Committee noted that the evidence on addiction liability was negative for each of them. The Committee decided, however, to make no recommendation with respect to their control at this time, but proposed that a very close watch be kept on further experimentation and any clinical use of these compounds.

* * *

The following drugs, in pursuance of the views communicated by the World Health Organization, were accordingly brought under international control by notification of the Secretary-General dated 21 December 1955 :

(*a*) To 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine;
3-diethylamino-1,1-di(2'-thionyl)-1-butene (proposed international non-proprietary name : diethylthiambutene);
3-hydroxy-N-phenethylmorphinan;
4-morpholino-2,2-diphenyl ethyl butyrate ;
and all of their respective salts

was applied the regime laid down in the 1931 Convention for the drugs specified in Article 1, Paragraph 2, Group I, of that Convention;

(*b*) To 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane and its salts

was applied the regime laid down in the 1931 Convention for the drugs specified in Article 1, Paragraph 2, Group II, of that Convention.

Abuse of Amphetamine

The Committee took note of the memorandum presented by Dr T. Masaki on the amphetamine problem in Japan, and had its attention drawn to the occurrence of abuse of amphetamine and amphetamine-like substances in other areas to an extent which constitutes a hazard to public health. The Committee noted that stern measures are already being taken by one of the governments concerned to meet the situation, and that suggestions have been made for local measures for improvement in other areas. The Committee proposed, as it had done previously, to keep close watch on the situation, but was of the opinion that abuse of amphetamine continued to be a local problem and not one for international action.

Pethidine

The Committee took note of the replies which had been received to the circular letter of the Director-General, pursuant to its recommendation,[11] bringing to the attention of governments and the medical profession throughout the world the dangerousness of the addiction potentiality of pethidine and the need for care in its use as with morphine.

[10] Proposed international non-proprietary name; approved common name in the United Kingdom of Great Britain and Northern Ireland.

[11] *Wld Hlth Org. techn. Rep. Ser.*, 1955, *95*, 10 (section 7.3.2).

The replies indicate a willingness to assist in the implementation of the warning. The Committee was pleased to note the publication of the warning in a number of medical journals and the intent of the World Medical Association to prepare a document on the subject for distribution to all national medical associations.

The Committee drew attention to one source of difficulty in the recognition of the danger with respect to pethidine, namely, the multiplicity of names under which the drug is marketed, so that, in some instances at least, the physician is not aware that the drug with which he is dealing is in fact pethidine. The same difficulty can arise when a new drug which is liable to produce addiction is introduced in different countries under different names.

The Committee was of the opinion that the difficulty could be met, as is already done in some countries, by the identification of the new drug in each instance by its recommended (or proposed) international non-proprietary name —for example, by the use of the international non-proprietary name on labels and in all descriptive matter—and suggested that WHO should consider the appropriateness of drawing the attention of governments to such a procedure.

In this connexion the Committee noted that the Commission on Narcotic Drugs had already recommended governments to use, whenever possible, in documents concerned with the implementation of the international treaties on narcotics, the non-proprietary names proposed by WHO in addition, where they so desire, to the chemical or proprietary names or both.[12]

International Non-Proprietary Names

The Committee was pleased to note the favourable response to the suggestions made at its fifth session,[13] and transmitted in the circular letter of the Director-General under the date of 21 April 1955, designed to speed up the selection of an international non-proprietary name for a drug which may come under international narcotics control. Replies from governments indicated that efforts are being made to implement the Committee's suggestions.

---

[12] *Wld Hlth Org., techn. Rep. Ser.*, 1952, *57*, 12 (section 10).

[13] *Wld Hlth Org., techn. Rep. Ser.*, 1955, *95*, 11 (section 10).

Bibliography

SYNTHETIC NARCOTIC DRUGS

Introduction

The Bulletin on Narcotics first published a bibliography on synthetic narcotic drugs in Volume III, No. 2, followed by another more comprehensive one in Volume VI, No. 2, and Volume VI, No. 3-4. It is felt, however, that the abundance of new material makes it worthwhile to publish at this time an additional bibliography on the same subject.

This bibliography has no claim to be complete, and information regarding books or articles not included in it would be gratefully received by the Division of Narcotic Drugs, Department of Economic and Social Affairs, European Office of the United Nations, Geneva, Switzerland. As before, this bibliography has been arranged by subject in the following way :

A. General works
B. Pethidine and related compounds
C. Methadone and related compounds
D. Morphinan and morphine synthesis
E. Dithienylbutenylamines and miscellaneous synthetics

Under each heading, publications are arranged alphabetically by author. Owing to the nature of the sources available to the secretariat for preparing this bibliography, several titles are given in translation only. They are preceded by an asterisk.

A. General Works

A

ANONYMUS : Expert Committee on Drugs Liable to Produce Addiction. Fifth report. *World Health Organization Technical Report Series*, 1955, *95*, p 1-16.

B

BADGER, G. M.; COOK, J. W.; DONALD, G. M. S.; GRAHAM, J. D. P.; WALKER, T.: Synthetic Analgesics. *Nature*, 1948, *162* : 4105, p. 21.

BECKETT, A. H.; CASY, A. F.: Stereochemistry of certain analgesics. *Nature*, 1954, 173, p. 1231-1232.

———; ———: Synthetic analgesics : stereochemical considerations. *Journal of Pharmacy and Pharmacology*, 1954, *6*, p. 986-1001.

BERGEL, F.; MORRISON, A. L.: Synthetic Analgesics. *Quarterly Review*, 1948, *2* : 4, p. 319-382.

BRAENDEN, O. J.; WOLFF, P. O.: Synthetic substances with morphine-like effect. *Bulletin of the World Health Organization*, 1954, 7 : 10, p. 1-25.

D

DONATELLI, L.: Il dolore ed i farmaci antidolorifici (Pain and analgesic drugs). *Rassegna Internazionale di Clinica e Terapia*, 1955, *35* : 1, p. 11-19; *ibid. 35* : 2, p. 50-59; *ibid. 35* : 4, p. 128-134.

E

EISENBERG, W. V.: Microscopic tests for alkaloids and synthetics. *Journal of the Association of Official Agricultural Chemists*, 1955, *38*, p. 653-655.

G

GADDUM, J. H.: *Pharmacology*, 4th edition, xviii + 562 pp. illus. Oxford University Press, New York, 11. (1953).

* GEIST, G.: (Addiction dangers of synthetic analgesics). *Pharmazeutische Zeitung ver. Apotheker Zeitung*, 1953, *89*, p. 831-834.

H

* HAAS, H.: (Comparison of analgesics). *N. Sch. Archiv für experimentelle Pathologie und Pharmakologie*, 1955, *225*, p. 442-452.

HILDEBRANDT, F.; MATTHÄY, E.: Die Wirkung der starken Analgetica Polamidon, Polamidon C (Polamivet) und Dromoran auf die Darmmotilität. (The effect of powerful analgesics, such as polamidone and polamidone C (polamivet) and dromoran on intestinal motility). *N. Sch. Archiv für experimentelle Pathologie und Pharmakologie*, 1954, *221* : 5, p. 399-403.

K

* KUDAKOVA, N. A.: (Use of non-exchange resins in the determination of pharmaceuticals). *Aptechnoe Delo*, 1955, *4* : 4, p. 34-37.

L

LESPAGNOL, A.: Les analgésiques centraux de synthèse. Les succédanés synthétiques de l'opium. *Actualités pharmacologiques*, 1949, *1*, p. 145-161; *ibid.*, 1951, *3*, p. 27-47.

LEWENSTEIN, Mozels J.: The preparation of compounds having a narcotic effect. British Patent, No. 713675 18 August 1954.

LEWIS, J. R.: A study of the development of tolerance to the actions of l-Methyl-4-(3-hydroxyphenyl)-4-piperidyl ethyl ketone hydrochloride in dogs. *Journal of Pharmacology and Experimental Therapeutics*, 1949, *96* : 4, p. 410-415.

———; The development of tolerance in rats to some new synthetic analgesics. *Journal of Pharmacology and Experimental Therapeutics*, 1949, *96* : 1, p. 31-37.

LUNDY, J. S.: Development of Analgesia after a century of anesthesia. *Journal of the American Medical Association*, 1955, *157* : 16, p. 1399-1403.

M

MACDONALD A. D.: Le soulagement de la douleur. *Annales Pharmaceutiques Françaises*, 1954, *12* : 9-10, p. 663-671.

MAROLDA, C. I.: Analgésicos centrales sintéticos (Synthetic central analgesics). *Semana Médica*, 1955, *106* : 11, p. 292-297.

MARTINETTO, G.: (Synthetic analgesics for pre-anesthetic treatment). *Minerva Anestesiologica*, 1955, *21*, p. 86-91.

MERGER, R.; LEVY, J.; BOURRICHON : Effets sur le travail de l'accouchement de l'association analgésique nembutal-dolosal-trilène. *Bulletin de la fédération des sociétés de gynécologie et d'obstétrique de langue française*, 1953, *5* : 3, p. 304-306.

———; MELCHIOR, J.: L'Analgésie obstétricale par l'association médicamenteuse : nembutal-dolosal-trilène. *Bulletin de la fédération des sociétés de gynécologie et d'obstétrique de langue française*, 1953, *5* : 5. p. 301-304.

MILLER, J. W.; ELLIOTT, H. W.: Rat tissue levels of carbon-14 labeled analgetics as related to pharmacological activity. *Journal of Pharmacology and Experimental Therapeutics*, 1955, *113* : 3, p. 283-291.

MORRISON, A. L.; RINDERKNECHT, H.: Synthetic Analgesics. *Jubilee Volume Emil Barell* (Hoffmann-La Roche), 1946, p. 253-263.

O

ORTH, O. S.: Newer drugs for general anesthesia. *Postgraduate Medicine*, 1954, *15* : 5, p. 393-398.

P

PÓRSZÁSZ, J.; KNOLL, J.; KOMLÓS, E.: Wirkung der Parasympathomimetika auf die Analgesie (Effect of parasympathetic substances on analgesia). *Acta Physiologica Academiae Scientiarum Hungariae*, 1951, *2* : 3-4, p. 469-477.

S

SCHAUMANN, O.: Die Wirkungsspezifität der morphinähnlichen Analgetica (Specificity of action of morphine-like analgetics). *Arzneimittel-Forschung*, 1954, *4* : 3a (special), p. 115-116.

* ———; (150 years of morphine and 15 years of synthetic morphine-like analgetics). *Angewandte Chemie*, 1954, *66*, p. 765-768.

SOEHRING. K.: Neuere synthetische Arzneimittel mit zentralanalgetischer Wirkung (New synthetic drugs with central analgesic action). *Medizinische Klinik*, 1950, *45* : 27, p. 817-822.

T

THORP, R. H.: The assessment of analgesic activity in new synthetic drugs. *British Journal of Pharmacology and Chemotherapy*, 1946, *1* : 2, p. 113-126.

TSAO, Yer Fang : The preparation of analogs of demerol, amidone, and isoamidone and the reactions of certain nitriles with Grignard reagents. University Microfilms (Ann Arbor, Mich.). Pub. No. 5752, 128 pp.; *Dissertations abstracts*, 1953, *13* : 5, p. 2061.

TSUTOMU, E.: Biochemistry of the poisoning with narcotics. *Shizen* (*Nature*), 1954, *9* : 5, p. 30-39.

V

VIDIC, E.; BREINLICH, J.: Zum mikrochemischen Nachweis von Cliradon und Dromoran im Urin (Microchemical determination of cliradon and dromoran in urine). *Arzneimittel-Forschung*, 1953, *3* : 9, p. 490-491.

W

WALSCH, E. O. F.: Habit-forming drugs and cell metabolism. *Pharmaceutical Journal*, 1954, 119, p. 483-484.

B. Pethidine and Related Compounds

A

ANDERSEN, H. C.; JEPSEN, O.; KRISTIANSEN, F.: Nystagmus induced by pethidine. *Acta Oto-Laryngologica*, Supplementum, 1953, 109, p. 9-14.

AREZIO, G.; PERUZZO, L.; VERGA, G.: Azione dei farmaci componenti il cocktail vegetativolitico (cloropromazina, prometazina, mefedina), somministrati isolamente, sul surrene di ratto (Action of the lytic cocktail drugs [chlorpromazine, promethazine, mephedine] administered separately, on the adrenal glands of rats). *Acta Anaesthesiologica*, 1955, *6* : 1, p. 1-10.

ARGENT, D. E.; DINNICK, O. P.: Pethidine phlebitis. *British Journal of Anaesthesia*, 1954, *26* : 4, p. 260-263.

AVISON, A. W. D.; MORRISON, A. L.: Synthetic Analgesics. VI. The synthesis of ketobemidone. *Journal of the Chemical Society*, 1950, p. 1469-1471. VII. Metadine and related 3-phenyl piperidine derivatives (4304) p. 1471-1474, No. 305. VIII. Further attempts to prepare 3-phenylpiperidine derivatives, p. 1474-1477.

B

BACHRACH, E. H.; GODHOLM, A. N.; BETCHER, A. M.: Clinical observations on the use of alphaprodine (nisentil) for postoperative analgesia. *Surgery*, 1955, *37* : 3, p. 440-445.

BADGER, G. M; COOK, J. W.; WALKER, T.: Synthesis of Piperidine derivatives. II. Aryldecahydroquinolines. *Journal of the Chemical Society*, 1948, II, p. 2011-2017.

———; COOK, J. W.; CROSBIE, G. W.: The chloromethylation of naphtalene and of Tebalin. *Journal of the Chemical Society*, 1947, II. p. 1432-1434.

BALIAH, V.; GOPALAKRISHNAN, V.: Synthesis of some 4-piperidone derivatives. *Journal of the Indian Chemical Society*, 1954, *31*, p. 250-252.

BARR, W.; COOK, J. W.: Synthesis of Piperidine derivatives, part I. *Journal of the Chemical Society*, 1945, I. p. 438-441.

BATTERMANN, R. C.: Clinical effectiveness and safety of a new synthetic analgesic drug, Demerol. *Archives of International Medicine*, 1943, *71* : 3, p. 345-356.

———; Demerol; a new synthetic analgesic : its indications as a substitute for morphine. *Connecticut Medical Journal*, 1944, *8* : 1, p. 13-17.

———; MULHOLLAND, J. H.: Demerol; a substitute for morphine in the treatment of postoperative pain. *Archives of Surgery*, 1943, *46* : 3, p. 404-409.

BAZANOVA, S. V.; KLEMENT'EV, F. V.; KISELEVA, K. I.: Sravuitel'noe deistvie atropina, lidola i tifena pri lechenii bol'nykh s diskineticheskimi zaporami (Comparative effects of atropin, lidol and thiphen in Therapy of diskinetic constipation). *Sovietskaia Meditsina*, 1954, *18* : 4, p. 29-31.

BAZANOVA, V. B. S. V.: Promedol—boleutoliaiushchee sredstbo pri lichenii vnutrennukh zabobevanuy (Promedol—analgesic in the treatment of internal disease). *Sovietskaia Meditsina*, 1954, *18* : 10, p. 39-40.

BELINKOFF, S.: Preoperative sedation with nisentil. *Current researches in Anesthesia and Analgesia*, 1955, *34* : 2, p. 116-118.

BENTHIN, W.: Schmerzlinderung in der Geburt durch Dolantin (Dolantin in delivery). *Deutsche Medizinische Wochenschrift*, 1940, *66*, p. 760-762.

BERGEL, F.; MORRISON, A. L.; RINDERKNECHT, H.: No. 69 Synthetic Analgesics. II. A new synthesis of Pethidine and similar compounds, p. 265-267; No. 70 III. The action of hydrogen halides on ethers of α α-bis-(B'hydroxyethyl) phenylacetonitrile, p. 267-269. No. 70 IV. Synthesis of 3-substituted piperidino and pyrrolidines, p. 269-272. *Journal of the Chemical Society*, 1944.

BIEL, J.H.; SPRENGELER, E. P.; LEISER, H. A.; HORNER, J.; DRUKKER, A.; & FRIEDMAN, H. L.: Antispasmodics. II. Derivatives of N-substituted-3-piperidols. *Journal of the American Chemical Society*, 1955, 77 : 8, p. 2250-2256.

BLICKE, F. F.; TSAO, E. P.: Preparation of l-methyl-4-phenyl-4-(aminomethyl)- and l-methyl-4-phenyl-4-(methylaminomethyl)-piperidine. *Journal of the American Chemical Society*, 1953, *75*, p. 5417-5418.

BRENDER, H.: Zur Pharmakologie der Phenyl-(l-piperidino)-essigsäure-ε-diäthylaminoäthylesters (Pharmacology of 2-(diethylamino-) ethyl phenyl piperidino-acetate). *Arzneimittel-Forschung*, 1954, *4* : 2, p. 67-70.

VON BRUECKE, S.: Ueber Dolantin Abusus und einen Fall von Dolantin delirium (Abuse of dolantin; a case of delirium caused by that drug). *Wiener klinische Wochenschrift*, 1940, *53*, p. 854-856.

BURNS, J. J.; BERGER, B. L.; LIEF, P. A.; WOLLACK, A.; etc.: The physiological disposition and fate of meperidine (demerol) in man and a method for its estimation in plasma. *Journal of pharmacology and experimental therapeutics*, 1955, *114* : 3, p. 289-298.

C

CALZOLARI, G.: Analgesia profonda ed anestesia locale nella chirurgia della tiroide (Deep analgesia and local anesthesia in thyroid surgery). *Minerva anestesiologica*, 1955, *21* : 6, p. 141-143.

CLARK, B. B.: The effect of syntropan, demerol, and trasentine on gastric secretion. *Federation Proceedings*, 1947, *6* : 1, Part I, p. 48.

CLIMENKO, D. R.: Demerol : A pharmacologically active substance with atropine-like and morphine-like properties. *Federation Proceedings*, 1942, *1*, p. 15.

COLLADOS STORNI, M. P.: Anestesia con petidina endovenosa para amigdalectomias; comunicacion prevista (Pethidine intravenous anesthesia in tonsillectomy; preliminary communication). *Revista de la Facultad de ciencias médicas de la Universidad nacional de Cordoba*, 1953, *11* : 3-6, p. 627-631.

COMINSKY, N. C.: The effect of demero and morphine on the histologic structure of mouse tissues. *Texas Reports on Biology and Medicine*, 1955, *13* : 2, p. 222-233.

COOK, A. H.; REED, K. J.: No. 98 : Experiments in the piperidine series. *Journal of the Chemical Society*, 1945, I, p. 399-402.

COSTA, P. J.; BONNYCASTLE, D. D.: The effect of levallorphan tartrate, nalorphine HCl and WIN 7681 (l-allyl-4-phenyl-4-carbethoxypiperidine) on respiratory depression and analgesia induced by some active analgetics. *Journal of Pharmacology and Experimental Therapeutics*, 1955, *113* : 3, p. 310-318.

CRIMENI, R.: Osservazioni cliniche sull'azione pre-anestetica del cliradon (Clinical observations on the pre-anesthetic effects of cliradon). *Gazzetta medica italiana*, 1953, *112* : 8, p. 203-206.

CRIPPS, J. A. R.; HALL, B.; HAULTAIN, W. F. T.: Analgesia in labour; record of 102 cases treated with pethidine. *British Medical Journal*, 1944, No. 4371, p. 498-500.

D

DEXEUS TRIAS DE BES J. M.; SEGUR FERRER, J. M.: La associación largactil-dolantina-pituitrina en la conducción del parto. (Combined largactil, dolantin and pituitrin in management of labour). *Revista Española de Obstetrica y Ginecologia*, 1955, *14* : 81, p. 132-137

DIETRICH, H.: Klinische Erfahrungen mit einem neuen synthetischen Spasmolyticum und Analgeticum (Clinical experiments with a new synthetic analgesic). *Deutsche medizinische Wochenschrift*, 1939, *65*, p. 969-970.

E

EIDINOVA, M. B.: Primenenie promedola pri zabolevaniakh nervnoi sistemi (Use of promedol in diseases of the nervous system). *Sovietskaia meditsina*, 1954, *18* : 11, p. 12-14.

ELLIOTT, H. W.: Comparative effects of l,l-diphenyl-l-(dimethylamino-isopropyl)-butemone-2 (10820) demerol and morphine on the respiration of rat cerebral cortex slices. *Federation Proceedings*, 1947, *6* Part II, p. 327-328.

ERLENDSSON, V.: Dolantin " Bayer ". *Ugeskrift for Laeger*, 1940, *102*; p. 1330-1331.

F

FEHER, V.; BRUTAR, V.: Užitĺ dolsinu pri porodu (Use of dolsin in labour). *Československá gynaekologie*, 1953, *18* : 4, p. 360-372.

FERRER, M. L.; SOKOLOFF, L.: The antidiuretic effect of morphine and Demerol in congestive heart failure. *American Journal of medical science*, 1947, *214* : 4, p. 372-384.

FERRON, M.: Nisentil; analgésique obstétrical. *Union Médicale du Canada*, 1955, *84* : 4, p. 431-433.

FINKELSTEIN, J.; LEE, J.: Piperidine derivatives. U. S. Patent No. 2,686,784, 17 August 1954 (Hoffmann-La Roche Inc.).

FITZGERALD, G.; McARDLE, B.: Effect of pethidine on pain in neurological cases. *Lancet*, 1943, No. 6236, p. 296-297.

FORTI, D.: Procaina e dolantinici per via endovenosa in anestesia ed analgesia postoperatoria (Intraveinous procaine and dolantin in anesthesia and postoperative analgesia). *Minerva Anestesiologica*, 1953, *19* : 8, p. 216-217.

FOSTER, R. H. L.; CARMAN, A. J.: Studies in analgesia : piperidine derivatives with morphine-like activities. *Journal of Pharmacology and Experimental Therapeutics*, 1949, *91* : 3, p. 195-209.

FROMMEL, E.; RADOUCO-THOMAS, C.: De l'incidence des ganglioplégiques sur la préparation de la narcose au pentothal par la morphine et le dolosal; du danger des opiacés. *Praxis*, 1955, *44* : 18, p. 407-409.

G

GALLEN. B.; PRESCOTT, F.: Pethidine as an obstetric analgesic—a report on 150 cases. *British Medical Journal*, 1944, No. 4335, p. 176-179.

GAMMELTOFT, A.; JOHANSEN, S. H.; RUBEN, H.: Pethidin ved cystoskopi; erfaringer med pethidin intravenost ved endoskopi af urethra og blaere hos maend (Pethidine in cystoscopy; experience with intravenous pethidine in endoscopy of male urethra and bladder). *Ugeskrift for Laeger*, 1953, *115* : 39, p. 1448-1449.

———; Intravenous pethidine for oesophagoscopy and gastroscopy. *Anaesthesia*, 1953, *8* : 3, p. 194.

GEFTER, A. I.; MATUSOVA, A. P.: Primenenie tifen-promedola pri koronarnoi bolezni (Use of tiphen-promedol in coronary disease). *Sovietskaia Meditsina*, 1955, *19* : 8, p. 22-25.

GLAZEBROOK, A. J.; BRANWOOD, A. W.: Clinical trials of 3-pethidine. *Lancet*, 1945, *249* : 6374, p. 528-529.

GORDON, G. S.; DIXON, A. B.: Observations on Demerol as an obstetric analgesic. *American Journal of Obstetrics and Gynecology*, 1943, *45*, p. 320.

* GREBENNIK, L. I.: (Elimination of promedol from the body). *Farmakologiya Toksikologiya*, 1954, *17* : 4, p. 48-51.

GYERMEK, L.: Studies on cholinergic blocking substances. VIII. Pharmacological actions of certain polymethylene-, bis- and azapentylene-bis-pyrrolidine and piperidine derivatives. *Acta Physiologica Academiae Scientiarum Hungaricae*, 1955, *8* : 1, p. 49-60.

H

HALLE, J.; DECHENE, J. P.; MONTMINY, L.; PARADIS, G.: Le nisentil en bronchoscopie. *Laval médical*, 1955, *20*: 1, p. 52-56.

HARDY, J. D.; McKEEN CATTELL : Measurement of pain threshold raising action of aspirin, codeine and meperidine (Demerol). *Federation Proceedings*, 1950, *9* : 1, Part I, p. 282.

HARVEY, W. P.; BERKMAN, F.; LEONARD, J.: Caution against the use of meperidine hydrochloride (isonipecaine, demerol) in patients with heart disease, particularly auricular flutter. *American Heart Journal*, 1955, *49* : 5, p. 758-769.

HECHT, H.; NOTH, P. H.; YONKMAN, F. F.: Demerol; clinical observations. *Journal of the American Medical Association*, 1943, *121* : 16, p. 1307.

HEIDT, T. J.; DALLIS, N. P.; O'CONNELL, W. J.: The use of Demerol in artificial fever. *American Journal of Psychiatry*, 1945, *101* : 6, p. 789-792.

HERSCHFUS, J. A.; SALOMON, A.; SEGAL, M. S.: The use of demerol in patients with bronchial asthma. *Annals of Internal Medicine*, 1954, *40* : 3, p. 506-515.

HOCH, D.; KARRER, P.: Synthèse de plusieurs homologues de la méthyl-pipéridine. *Helvetica Chimica Acta*, 1954, *37*, p. 397-402.

HORÁKOVÁ, Z.; VOTAVA, Z.: Analgetický úcinek morfinu, dolsinu a mecodinu pri ruzném zpusobu podání; farmakologická studie (Analgetic effect of morphine, dolsin and mecodin in various ways of application; a pharmacological study). *Ceskoslovenská Farmacie*, 1955, *4* : 3, p. 131-133.

HURLBUT, D. B.; DILLE, J. M.: The effect of nisentil upon the intra-uterine respiratory movements of the rabbit fetus. *Anesthesiology*, 1952, *13* : 1, p. 71-76.

———; ———: The effect of nisentil upon the intra-uterine respiratory movements of the rabbit fetus. *Journal of Pharmacology and Experimental Therapeutics*, 1951, *103* : 4, p. 348.

I

IZAR, G.; IENZI, S.: Studi sulla Dolantina. (Study on Dolantine). *Rassegna internaz. di clinica e terapia*, 1941, *22*, p. 213-221, 251-256.

J

JENSEN, K. A.; LUNDQUIST, F.; REKLING; WOLFFBRANDT, C. A.: Ein neuer Typus von Piperidin Derivaten mit analgeter und spasmolyter Wirkung (A new type of piperidine-derivative with analgesic and spasmolytic activity). *Chemisches Zentralblatt*, 1944, I. *115* : 5, p. 297-298.

JESSEN, H.: Dolantin in recurrent hiccups. *Journal of the American Medical Association*, 1942, *118* : 8, p. 674-675.

———; Om Dolantin. *Ugeskrift for Laeger*, 1940, *102*, p. 1326-1328.

K

KLEIN, E. K.: Erfahrungen mit Dolantin, einem myotrop und neurotrop wirkenden Spasmolytikum (Experience with Dolantin, a Spasmolytic working as myotrop and neurotrop). *Münchener medizinische Wochenschrift*, 1939 *2*, p. 1676.

KRACHEEL, E.: Die Leistungsfähigkeit der Blutnarkose, ein Beitrag zum Narkoseproblem der chirurgischen Praxis (Potentiation of intraveinous anesthesia, a contribution to the anesthesia problem of surgical practice). *Zentralblatt für Chirurgie*, 1955, *80* : 10, p. 398-405.

KUCHER, I.: Zwei Fälle von Dolantinsucht. (Two cases of addiction to dolantin). *Klinische Wochenschrift*, 1940, *19*; p. 688-689.

KUNZ, T.: Die Dolantin-Evipan-Lachgasnarkose mit My 301 als Muskelrelaxans (Dolantin-evipan nitrous oxide anesthesia with My 301 as a muscle relaxant). *Medizinische*, 1953, No. 48, p. 1555-1556.

KWARTLER, C. F.: U.S. patent No. 2,634,275, 7 April 1953. 4-acylamino-l-alkyl-4-phenylpiperidines and method of making same.

L

LAGARDE, L. A.; ORTIZ DE LA PENA, R.; BRAVO SERRADELL, O.: Tres drogas auxiliares en obstetricia (Three auxiliary drugs in obstetrics). *Ginecologia y Obstetricia de Mexico*, 1955, *10* : 2, p. 140-150.

LEE, J.; ZIERING, A.; BERGER, L.; HEINEMAN, S. D.: Studies on the synthesis of Analgesic compounds. *Jubilee Volume Emil Barell*, (Hoffmann-La Roche), 1946, p. 265-305.

LEWIS, J. R.: Action of l-methyl-4-(3-Hydroxy phenyl)-4-piperidyl ethyl ketone on the gastrointestinal tract. *Proceedings of the Society for Experimental Biology and Medicine*, 1949, *71* : 2, p. 300-303.

M

McELVAIN, S. M.; DICKINSON, W. B.; ATHEY, R.: Piperidine derivatives XXV. Reaction of certain 3-substitutes l-methyl-4-piperidones with organometallic compounds. *Journal of the American Chemical Society*, 1954, *76*, p. 5625-5633.

———; BERGER, R. S.: Piperidine derivatives. XXVII. The condensation of 4-piperidones and piperidinols with phenols. *Journal of the American Chemical Society*, 1955, *77* : 10, p. 2848-2850.

MARTIN, C.: L'anesthésie de base diparcol-dolosal en chirurgie gériatrique et chez le malade représentant un mauvais risque. *Anesthésie et Analgésie*, 1955, *12* : 2, p. 335-347.

Motatovo MATSUMOTO; Yasumichi KISHINOUXE; Iwao YAMAZAKI; Yoshio NAKAMURA : Synthesis of *N*-ethylpiperidine. *Coal Tar*, 1954, *6*, p. 198-201.

MOREL-FATIO, D.: A propos de 200 cas d'anesthésie de base (diparcol-dolosal) + locale en chirurgie réparatrice. *Anesthésie et Analgésie*, 1955, *12* : 2, p. 348-357.

MORISOT, D.: L'association diéthazine-péthidine I. V. (dipdol) comme anesthésie de base. *Anesthésie et Analgésie*, 1955, *12* : 2, p. 365-368.

N

NAZAROV, Z. N.; NOKOLOV, D. V.; RAKCHEEVA, V. N.: Geterotsiklicheskie soedinenula. XXX. Stereoizomeriia 2, 5-dimetil-4-piperidola, 1, 2, 5-trimetil-4-piperidola i ikh proizvodnykh (Heterocyclic compounds. XXIX. Stereoisomers of 2, 5-dimethyl-4-piperidol, 1, 2, 5-trimethyl-4-piperidol and their derivatives). *Izvestia Akademii Nauk SSSR otdelenie Khissicheskikh Nauk*, 1954, No. 1, p. 80-94.

NICKERSON, M.; GOODMAN, L. S.: Synergistic isonipecaine—amphetamine analgesia. *Federatiwo Proceedings*, 1947, *6* : 1, Part II, p. 360.

O

ORKIN, L. R.; EGGE, R. K., ROVENSTINE, E. A.: Effect of nisentil, meperidine and morphine on respiration in man. *Anesthesiology*, 1955, *16* : 5, p. 699-707.

P

PASSMORE, G. G.; SANTA CRUZ, E. W.: The use of intravenous and intramuscular injections of demerol and scopolamine in labor and delivery. *American Journal of Obstetrics and Gynecology*, 1954, *68* : 4, p. 998-1008.

PATERSON, S. J.; PRESCOTT, F.: Nalorphine in the prevention of neonatal asphyxia due to maternal sedation with pethidine. *Lancet*, 1954, *266* : 6810, p. 490-493.

PERRINE, T. D.; MAY, E. L.: Synthesis of 6-dimethylamino-4, 4-diphenyl-heptane and other compounds related to Demerol. *Journal of Organic Chemistry*, 1954, *19*, p. 773-779.

PÓRSZÁZ, J.; VENULET, J.; GIBSZER-PÓRSZÁSZ, K.: Untersuchungen über die Synergisierbarkeit der Analgetika; Wirkung des Doryls und Physostigmins auf die Verteilung des Dolantins im Organismus (Studies on synergism of analgesics; effect of doryl and physostigmine on the distribution of dolantin in the organism). *Acta physiologica academiae scientiarum hungaricae*, 1954, *5* : 3-4, p. 509-519.

PRESTON, F. S.: Anaesthesia for mitral valvotomy. *British Journal of anaesthesia*, 1953, *25* : 4, p. 299-314.

PRYOR, W. J.: Pethidine in anesthesia. *New Zealand Medical Journal*, 1953, *52* : 291, p. 398-400.

R

RANDALL, L. O.; LEHMANN, G.: Pharmacological studies on analgesic piperidine derivatives. *Journal of Pharmacology and Experimental Therapeutics*, 1948, *93* : 3, p. 314-328.

RASOR, R. W.; CRECRAFT, H. J.: Addiction to Meperidine (Demerol) hydrochloride. *Journal of the American Medical Association*, 1955, *157* : 8, p. 654-657.

REISINGER, F.: Das neue Analgeticum und Spasmolyticum Dolantin (A new analgesic and spasmolytic; dolantin). *Wiener medizinische Wochenschrift*, 1940, *90*, p. 400.

ROBERTS, H.; WRIGLEY, F.: Nisentil in obstetrics; clinical trials with a new analgesic. *Journal of Obstetrics and Gynaecology of the British Empire*, 1953, *60* : 4, p. 538-540.

ROBY, C.; SCHUMANN, W. R.; Demerol (S-140) and scopolamine in labor: a preliminary report. *American Journal of Obstetrics and Gynecology*, 1943, *45*, p. 318.

ROJAS, N.; BELBEY, J.: Hábito tóxico y dolantina (Drug addiction and dolantin). *Semana Médica*, 1941, *2*, p. 616-618.

ROSENTHAL, H.: Beobachtungen zur Bekämpfung des Wundschmerzes mit dem neuen Analgeticum Dolantin (Remarks on fighting traumatic pain with a new analgesic, Dolantin). *Münchener medizinische Wochenschrift*, 1939, *86*, p. 1079-1080.

ROST, H.; SIEVERT, C.: Die Einwirkung von Phenotiazinderivaten und Dolantin auf Diurese und Nierenclearance (Effects of phenothiazine derivatives and Dolantin on diuresis and kidney clearance). *Zentralblatt für Gynäkologie*, 1954, *76* : 49, p. 2148-2153.

ROUCHY, R.; BREIL, J. F.: Accouchement dirigé : la perfusion d'extrait post-hypophysaire associée ou non à d'autres médications. *Gynécologie et Obstétrique*, 1954, *53* : 3, p. 364-374.

RUDDY, A.W.; BISHOP, H.W.: Antispasmodics. III. N-methyl-2(4)-*W*-R-*w*-phenylaltyl piperidines and 2-R-2-Phenyl-4(5)-(N-methyl-4-piperidyl)-alkanenitriles. *Journal of the American Chemical Society*, 1952, *74* : 8, p. 1919-1921.

RUSTIA, G.; ALMEDA, L.: Demerol and scopolamine in obstetrics. *Journal of the Philippine Medical Association*, 1948, *24* : 2, p. 61-65.

RYPDAL, A.: Pethidin ved oesophagoskopi og bronchoskopi (Pethidine in oesophagoscopy and bronchoscopy). *Tidskrift for den Norske laegerforening*, 1953, *73* : 21, p. 809-812.

S

SCHAEFER, F.: Schmerzbekämpfung in der Chirurgie mit Dolantin (The suppression of pain in surgery through the use of dolantine). *Deutsche medizinische Wochenschrift*, 1939, *65*, p. 970-972.

SCHAUMANN, O.: Ueber eine neue Klasse von Verbindungen mit spasmolytischer und zentral-analgetischer Wirksamkeit unter besonderer Berücksichtigung des l-Methyl-4-phenyl-piperidin-4-carbonsäure-äthylesters (Dolantin) (A new class of compounds with spasmolytic and central analgesic action, particularly l-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester). *Archiv für experimentelle Pathologie und Pharmakologie*, 1940, *196* : 2, p. 109-136.

SCHIØLER, V.: Dolantin. *Ugeskrift for Laeger*, 1940, *102*, p. 1328-1330.

SCHLUNGBAUM, H.: Schmerzbekämpfung mit Dolantin, einem synthetischen hergestellten Spasmolytikum und Analgetikum (Suppression of pain through the use of dolantin, a synthetic spasmolytic and analgesic). *Medizinische Klinik*, 1939, *35*, p. 1259.

SCHMITT, W.: Klinische Prüfung einer neuen Piperidin-Verbindung als Schlafmittel (Clinical trial of a new piperidine compound as soporific) *Medizinische Klinik*, 1955, *50* : 29, p. 1223-1224.

SCHMUTZ, J.; KUNZLE, F.: l-Methyl-4-benzyl-piperidin-4-carbonsäure-äthylester und neue Synthese des l-Methyl-4-cyano-piperidins (l-methyl-4-benzyl-piperidine-4-carboxylic acid ethylester and new synthesis of l-methyl-4-cyanopiperidine). *Helvetica chimica Acta*, 1955, *38* : 4, p. 925-930.

* SCHWARKE, R.: (Addiction to Dolantin). *Deutsche Zeitschrift für die gesamte gerichtliche Medizin*, 1941, *25*, p. 17-23.

SCOTT, D.L.: Pethidine and gallamine alone in the treatment of fractured mandible. *British Journal of Anaesthesia*, 1955, *27* : 7, p. 393-397.

SHARTS, S. E.: KOTOVA, E. S.: Promedol v oftalmologicheskoi praktike (Promedol in ophthalmologic practice). *Sovietskaia Meditsina*, 1955, *19* : 2, p. 75-77.

SIGIDIN, I. A.: O boleutoliaiushtchem preparate promedole (The analgesic preparation promedol). *Sovietskaia Meditsina*, 1953, *17* :10, p. 25-27.

SOKOLOV, I.V.: Primenenie tifen-promedola pri stenokardii i nekotorykh drugikh zabolevaniiakh (Use of tiphen-promedol in stenocardia and some other diseases. Emploi du tiphen-promedol en stenocardie et quelques autres affections). *Sovietskaia Meditsina*, 1955, *19* : 8, p. 26-28.

SONNEK, W.: Geburtserleichterung durch Dolantin (Use of dolantin in obstetrics). *Deutsche medizinische Wochenschrift*, 1941, *67* : 32, p. 868-871.

SOSTMAN, A.: Zur Ablösung des Morphin und seiner Abkömmlinge in der Gynäkologie durch Dolantin (Elimination of morphine and its derivatives in gynecology by means of Dolantin). *Medizinische Welt*, 1940, *14*, p. 325.

SPITZER, W.: Obstetric analgesia with pethidine. *British Medical Journal*, 1944, No. 4335, p. 179-181.

SPROCKHOFF, O.: Dolantin in der Kinderheilkunde (Dolantin in pediatrics). *Deutsche medizinische Wochenschrift*, 1941, *67*, p. 383.

STAHNKE, H. L.: Demerol as an anti-scorpion therapeutic agent. *Arizona Medicine*, 1954, *11* : 2, p. 51-52.

STROUD, M. W. III; LAMBERTSEN, C. J.; EWING, J. H.; KOUGH, R. H.; GOULD, R. A.; SCHMIDT, C. F.: The effects of aminophylline and meperidine alone and in combination on the respiratory response to carbon dioxide inhalation. *Journal of Pharmacology and Experimental Therapeutics*, 1955, *114* : 4, p. 461-469.

SWERDLOW, M; FOLDES, F. F.; SIKER, E. S.: The effects of nisentil hydrochloride and levallorphan tartrate on cerebrospinal fluid pressure. *British Journal of Anaesthesia*, 1955, *27* : 5, p. 244-249.

———; ———; ———; The effects of nisentil HCl (alphaprodine HCl) and levallorphan tartrate on respiration. *American Journal of the Medical Sciences*, 1955, *230* : 3, p. 237-250.

SZIRMAI, E.: Der Zusammenhang zwischen der Blutgerinnung und der schmerzstillenden Wirkung des Dolantins (Relation between blood coagulation and palliative effect of Dolantin). *Pharmazie*, 1955, *10* : 1, p. 14-18.

* ———; BASUSZ, E.; NYIRI, I.: (Action of the new analgesic agent Depridol on pain sensation, duration of childbirth, and efficiency of parturition). *Pharmazie*, 1954, *9*, p. 116-123.

T

TEARE, F. W; HUSTON, M. J.: Effect of certain drugs on skeletal muscle. *Archives internationales de pharmacodynamie et de thérapie*, 1953, *95* : 3-4, p. 437-443.

TRIFILIO, A. A.; HUDSON, P. B.: A clinical study of 100 cases in which nisentil hydrochloride was used for analgesia to facilitate cystoscopy and other urological procedures. *Journal of Urology*, 1955, *74* : 2, p. 246-251.

TRIPOD, J.; SURY, E.; HOFFMANN, K.: Zentralerregende Wirkung eines neuen Piperidinderivates (Analeptic effect of a new piperidine derivative). *Experientia*, 1954, *10* : 6, p. 261-262.

TUTWILER, F. B.; CHILD, R. G.; WRENN, S. N.: Potential analgesics and antispasmodics. I. Synthesis of open-chain analogs of Demerol. *Journal of Organic Chemistry*, 1954, *19*, p. 910-918.

V

VIDIC, E.: Der Nachweis von Polamidon und Dolantin im Urin und ihre Trennung vom Morphin (Determination of Polamidon and Dolantine in urine and their separation from morphine). *Archiv für experimentelle Pathologie und Pharmakologie*, 1951, *212* : 5-6, p. 339-351.

VOEVODINA, O. N.: Vliianie Promedola na uslovnoreflektornuiu decatel'nost' (Influence

of promedol on conditioned reflex action). *Farmakologiya i Toksikologiya*, 1954, *17* : 1, p. 8-12.

VOGT, K.E.: Dolantin zur Schmerzbekämpfung bei inneren Erkrankungen (Dolantin for pain control in internal diseases). *Medizinische Klinik*, 1940, *23*, p. 622.

W

WALTON, E.; GREEN, M. B.: Search for new analgesics. I. Homologs of pethidine and related compounds. *Journal of the Chemical Society*, 1945, I, p. 315-319.

WAY; GRUBBS, R. C.; SWANSON, R.: The effects of isonipecaine (demerol) on auricular fibrillation. *Federation Proceedings*, 1947, *6* : 1, Part II, p. 382.

WAY, E. L.; GIMBLE, A. I.; LIGON Jr. E. W.: The tissue distribution of isonipecaine (demerol) *Federation Proceedings*, 1947, *6* : 1, Part II, p. 381-382.

WAY, E.L.; BINDER, S. S.; MICHAEL, A. H. One way isonipecaine irimethadione antagonism. *Federation Proceedings*, 1947, *6* : 1, Part II, p. 381.

WEINER, E.: Nisentil; a new basal analgesic for oral surgery. *International Journal of Anesthesia*, 1955, *2* : 4, p. 245-249.

WIDDOWSON, H. R.; AQUINO, T. D.; VIRTUE, R. W.: Recovery time following demerol or pentothal supplementation of nitrous oxide anesthesia. *Anesthesiology*, 1955, *16* : 5, p. 747-750.

WIEDER, H.: Addiction to meperidine hydrochloride (demerol hydrochloride). Report of 3 cases. *Journal of the American Medical Association*, 1946, *132* : 17, p. 1066-1068.

WINDER, A. V.: A preliminary test for analgetic action in guinea pigs (morphine, demerol). *Archives internationales de pharmacodynamie et de thérapie*, 1947, *74* : 2, p. 176-192.

———; Quantitative evaluation of analgetic action in guinea pigs. Morphine ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (Demerol) + acetylsalicylic acid. *Archives internationales de pharmacodynamie et de thérapie*, 1947, *74* : 3/4, p. 219-232.

WULFSOHN, N. L.: Intravenous pethidine for hiccup. *Lancet*, 1954, *267* : 6832, p. 289.

Y

YONKMAN, F. F.; NOTH, P. H.; HECHT, H. H.: Some pharmacologic features of Demerol. *Proceedings of the Central Society for Clinical Research*, 1942, *15*, p. 89-90.

Z

ZHEREBTSOV, L. A.: Klinicheskoe issledovanie novogo obezbolivaiushchego preparata izopromedola (Clinical evaluation of a new analgetic preparation [isopromedol]). *Sovietskaia Meditsina*, 1955, *19* : 8, p. 29-33.

C. Methadone and related compounds

A

ANOSOV, N. N.; PISSAREVA, N. A.: Lechanie fenadonom bol'nykh s nevralgicheskim sindronom razlichnogo proiskhozhdeniia (Therapy of neuralgic syndromes of various origins with phenadon). *Sovietskaia Meditsina*, 1954, *18* : 11, p. 11-12.

ANWEILER. H.: Biologischer Nachweis von Polamidonabusus (Biological detection of polamidon addiction). *Klinische Wochenschrift*, 1954, *32* : 5-6, p. 138-139.

B

BECKETT, A. H.; CASY, A. F.: The structure of 6-methylmethadone. *Journal of Pharmacy and Pharmacology*, 1955, 7 : 3, p. 204-206.

BLICKE, F. F.; TSAO, E. P.: Preparation of several analogs of amidone and isoamidone. *Journal of the American Chemical Society*, 1954, *76*, p. 2203-2206.

BURROUGHS, H. E.: Methadone narcosis in dogs. *Journal of Small Animal Medicine*, 1953, *1* : 7, p. 301-303.

C

COOK, L.; NAVIS, G.; FELLOWS, E. J.: Enhancement of the action of certain analgesic drugs by diethylamino ethyl 2,2-diphenylvalerate hydrochloride (SKF 525-A). *Journal of Pharmacology and Experimental Therapeutics*, 1954, *112*, p. 473-479.

E

EASTON, N. R.: Structure of isoamidone. *Journal of the American Chemical Society*, 1954, *74*, p. 5772.

———; FISH, V. B.: Synthesis of 5-dimethylamino-4,4-diphenyl-2-pentanol. *American Chemical Society, 126th Meeting*, 1954, p. 27N-28N.

———; ———; Decomposition of quaternary salts. II Stereospecificity in the isomethadone series. *Journal of the American Chemical Society*, 1954, *76*, p. 2836-2837.

EDDY, N. B.: A new morphine-like analgesic. *Journal of the American Pharmaceutical Association*, 1947, *8* : 11, p. 536-540.

G

GERO, H.: Steric considerations on the chemical structure and physiological activity of methadone and related compounds. *Science*, 1954, *199* : 3082, p. 112-113.

GRIEBEL, C.: Nachweis von Polamidon (Determination of Polamidon). *Pharmazeutische Zeitung*, 1950, *86*, p. 540.

H

HAIBACH, A.: Gibt es eine Ticardasucht? (Ticarda addiction). *Deutsches medizinisches Journal*, 1955, *6* : 3-4, p. 117-119.

HERR, F.; PÉRSZÁSZ, J.: Uber die Wirkung einiger Derivate des Polamidons (Action of some derivates of polamidon). *Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie*, 1950, *210* : 3, p. 294-304.

HOFFMANN, W.: Die Analytik des Polamidon (Analysis of polamidone). *Arzneimittel-Forschung*, 1953, *3* : 7, p. 364-368.

———; Der Nachweis des Polamidon in Postonalsuppositorien (Detection of Polamidon in postonal suppositories). *Arzneimittel-Forschung*, 1953, *3* : 8, p. 440-441.

HOWE, E. E.; BROOK, B.; TISHLER, M.: Salts of D-amidone with an optically active acid and process for revolving DL-amidone. *U.S. Patent* No. 2,644,010, 1953.

I

ISBELL, H.; FRASER, H. F.: Addictive properties of methadone derivatives. *Federation Proceedings*, 1954, *13* : 1, Part 1, p. 369-370.

K

* KNOBLAUCH, G.; KRAUSE, D.: (Experimental and clinical investigations on the effect of polamidone [methadone] on the dog). *Tierärztliche Umschau*, 1950, *5*, p. 134-138.

L

LEIMBACH, D. G.; EDDY, N. B.: Synthetic analgesis. III. Methadols, isomethadols and their acyl derivatives. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *110* : 2, p. 135-147.

M

MAY, E. L.; PERRINE, T. D.: Wagner rearrangement of α-DL-6-dimethylamino-4, 4-diphenyl-3-heptonal (α-DL-methadol). *Journal of Organic Chemistry*, 1953, *18*, p. 1572-1577.

MILLER, J. W; ELLIOTT, H. W.: *In vitro* studies on the diphasic action of methadone. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *110* : 1, p. 106-114.

O

OSTERWALD, K. H.: Zwei Beobachtungen von Atemlähmung nach Polamidonmissbrauch (Two observations of respiratory paralysis after overdose of polamidone). *Sammlung von Vergiftungsfällen; Archiv für Toxicologie*, 1953, *14* : 6, p. 349-351.

P

* PAVLOVA, N. IA.: (Action of phenadone on the bloodvessels of the detached rabbit ear [not unnerved]). *Farmakologiia i Toksicologiia*, 1955, 18 : 1, p. 27-28.

PERRINE, T. D.: Synthesis of compounds related to the methadols. *Journal of Organic Chemistry*, 1953, *18* : 7, p. 898-903.

PHATAK, N. M.; DAVID, N. A.: Addiction potentialities of some methadone analgesics and alpha acetylmethadol as determined by their hyperglycemic responses in rabbits. *Current Researches in Anesthesia and Analgesia*, 1953, *32* : 4, p. 242-249.

PIOTTI, F.: Nouveaux analogues du chlorhydrate de méthylamino 4-4-dyphényl-3-heptanone. *Minerva Medica*, 1951, I, p. 449-451.

PRATT, J. H.; WELCH, J. S.: Hyatrobal and methadone hydrochloride in preoperative preparation of patients. *Journal of the American Medical Association*, 1955, *157* : 3, p. 231-234.

R

RODÉS DE SISTERNES, L.: Analgesia en el parto con methadon-escopolamina (Methadon-scopolamine analgesia in labour). *Toko-Ginecología Práctica*, 1955, *14* : 133, p. 295-299.

S

SALM, H.: Beobachtungen bei Polamidonsüchtigen, insbesondere über psychische Veränderungen nach Polamidonmissbrauch (Observations on polamidon addiction, especially on psychic changes after misuse of polamidon). *Nervenarzt*, 1953, *24* : 4, p. 143-148.

SALVESEN, B.: Methadon Fargereaksjoner og fotometrisk bestemmelse (Methadone colour

reactions and photometric estimation). *Meddelelser fra Norsk famaceutisk selskap*, 1952, *14*, p. 1-11.

SCHILDKNECHT, E. A.; BROWN, E. V.: Synthesis of 2-thiopene analogs of amidone and isoamidone. *American Chemical Society, Abstract of papers, 126th meeting*, 1954, p. 27N-28N.

SLETZINGER, M; CHAMBERLIN, E. M.; TISHIER, M.: Synthesis of isomethadone. *Journal of the American Chemical Society*, 1952, *74* : 22, p. 5619-5620.

———; TISHLER, M.: Resolution of isoamidone with (Lx)-p-nitrobenzoyl-glutanic acid. *U.S. Patent* No. 2,625,564, 1954.

SPEETER. M. E.: Amidone amines and related derivatives. *U.S.Patent* No. 2,632,762, 1954.

STEPHAN, W.: Polamidon in der Behandlung des Tetanus (Polamidon in tetanus treatment). *Die Medizinische*, 1953, No. 31-32, p. 1009-1011.

STOUGHTON, R. W.: An isomer of amidone. *U.S. Patent* No. 2,670,375, 1954.

SUNG, C. Y.; WAY, E. L.: The fate of the optical isomers of alpha acetyl methadol. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *110* : 3, p. 260-270.

V

VIDIC, E.: Der Nachweis von Polamidon und Dolantin im Urin und ihre Trennung vom Morphin (Determination of Polamidon and Dolantin in the urine and their separation from Morphine). *Archiv für experimentelle Pathologie und Pharmakologie*, 1951, *212* : 5-6, p. 339-351.

W

WALTON, E.; OFNER, P.; THORP, R. H.: New analgesics. III. Homologs of amidone, isoamidone, and some related compounds. *Journal of the Chemical Society*, 1949, p. 648-655.

Z

ZAUGG, H. E.; HORROM, B. W.; VERNSTEN, M. R.: The Mannich reaction of diphenylacetonitrile. Products and derivatives. *Journal of the American Chemical Society*, 1953, *75* : 2, p. 288-291.

D. Morphinan and morphine synthesis

A

AKCASU, A.: Yoni bir analjezik drog metorphinana (Dromoran Roche) (A new analgesic, 3-hydroxy-N-methylmorphinan [Dromoran Roche]). *Tip fakültesi mecmuasi*, 1954, *17* : 4, p. 530-536.

ANONYMOUS : New approved drugs l levorphan tartrate, levo-dromoran tartrate, etc. *University of Michigan Medical Bulletin*, 1954, *20* : 1, p. 22-25.

B

BAGGESGAARD-RASMUSSEN, H.: Om morphinets konstitution og syntese samt om nogle syntetiske analgetica (Constitution and synthesis of morphine and some synthetic analgesics). *Dansk tidskrift for farmaci*, 1954, *28* : 7, p. 133-155.

BELLEAU, B.: A new synthetic approach to the morphine structure. *Journal of the American chemical society*, 1953, *75* : 5, p. 1159-1163.

BOZZA, M.: L'N-metil-morfinano a complemento dell'anestesia N_2O-O_2-pentothal (N-methylmorphinan as adjuvant in nitrous oxide-oxygen-pentothal anesthesia). *Minerva chirurgica*, 1954, *9* : 7, p. 319-327.

BREZINSKI, J. J.: Use of the internal Michael reaction in the synthesis of morphine analogs. *University microfilms*, Publ. No. 10046, 108 pp. *Dissertation Abstracts*, 1954, *14*, p. 1921-1922.

BROSSI, A.; HAEFLIHER, O.; SCHNIDER, O.: Oxy-morphinane. 6. Die papierchromatographische Bestimmung von Morphinanderivaten und die Verfolgung ihrer Ausscheidung beim Hund (Hydroxy-morphinan : 6. Paper chromatography of morphinan derivatives and their excretion in urine). *Arzneimittel-Forschung*, 1955, *5* : 2, p. 62-66.

BROWN, A. K.: Levorphan in anaesthesia. *British Medical Journal*, 1954, No. 4894, p. 967-969.

C

CALDERONI, C.; CAVACIUTI, P.: L'idrossi-N-metil-morfinano in anestesia per interventi di chirurgia plastica (3-hydroxy-N-methylmorphinan in anesthesia for plastic surgery). *Ospedale maggiore*, 1955, *43* : 5, p. 231-234.

CALIGARI, G.: Il tartrato di 3-ossi-N-metilmorfinano (dromoran) nella pratica clinica (3-hydroxy-N-methylmorphinan tartrate [dromoran] in clinical practice). *Gazetta medica italiana*, 1955, *114* : 5, p. 113-116.

* CANDELERO, G.; CARPINO, A.: (Tartrate of 3-hydroxy-N-methylmorphinan as preanesthetic and support anesthesia in neurosurgery). *Policlinico*, 1955, *63* : p. 247-258.

CAPPELLO, G.; DI PASQUALE, S. : Traitement de la toux avec le bromhydrate de dextrométhorphane (Romilar) en tuberculose. *Schweizerische Zeitschrift für Tuberkulose*, 1955, *12* : 1, p. 80-88.

CASS, L. J.; FREDERICK, W. S.: Evaluation of a new antitussive agent (dextro-3-methoxy-N-methylmorphinan hydrobromide). *New England Journal of medicine*, 1953, *249* : 4, p. 132-136.

COSTA, P. J.; BONNYCASTLE, D. D.: Effect of levallorphan tartrate, Nalorphine HCl and WIN 7681 (l-Allyl-4-phenyl-4-Carbethoxypiperidine) on respiratory depression and analgesia induced by some active analgetics. *Journal of pharmacology and experimental therapeutics*, 1955, *113* : 3, p. 310-318.

COUNCIL on pharmacy and chemistry : New and unofficial remedies : levorphane tartrate. *Journal of the American medical association*, 1954, *156* : 3, p. 250-251.

CREHAN, A.: Methorphinan as a supplementary anaesthetic medium. *Journal of the Irish medical association*, 1954, *34* : 201, p. 74-75.

E

ELAD, D.; GINSBURG, D.: Synthesis of morphine. *Journal of the American chemical society*, 1954, *76*, p. 312-313.

———; : Synthesis in the morphine series. VI. Synthesis of morphine. *Journal of the chemical society*, 1954, p. 3052-3056; *Chemical abstracts*, *48*, 12056 b.

EMANUELLI, H.; MACCAGNO, V.: L'uso del tartrato di 3-idrossi-N-metilmorfinano quale prenarcotico (Use of 3-hydroxy-N-methylmorphinan tartrate as pre-narcotic. Emploi du tartrate d'hydroxy-3-N-méthylmorphinane comme pré-anesthésique). *Acta anaesthesiologica*, 1955, *6* : 2, p. 151-156.

EMMONS, M. S.; GOSLIN, F. B.; SAFLEY, M. W.; TIDRICK, R. T.: Use of levorphan tartrate for relief of postoperative pain; preliminary report. *Journal-Lancet*, 1955, *75* : 1, p. 29-31.

* ENGELMEIER, M. P.: (Attempted suicide with E605 and treatment with an allyl derivative of the morphinan group). *Medizinische Klinik*, 1954, *49*, p. 1996-1998.

ERNE, K.: Den första morfinsyntesen genomförd (The first synthesis of morphine). *Farmacevtisk Revy*, 1952, *51*, p. 289-294.

F

FARBENFABRIKEN BAYER : Verfahren zur Herstellung von l-benzyl-1,2,3,4,5,6,7,8-oktahydro-isochinolin (Process for manufacture of l-benzyl-1,2,3,4,5,6,7,8-octahydro-isoquinolin). *Swiss Patent* 289377, 1 July 1953.

G

GAARD, R. C.: Postoperative use of levo-dromoran tartrate. *Journal-Lancet*, 1955, *75* : 7, p. 309-310.

GROSS, E. G.; HAMILTON, W. K.: Preliminary observations on the effect of levallorphan on respiratory depression and analgesia of levorphan in man. *Journal of laboratory and clinical medicine*, 1954, *43* : 6, p. 938-941.

GRUBER, C. M. Jr.: Effect of levallorphan tartrate upon the toxicity of morphine. *Proceedings of the Society for experimental biology and medicine*, 1955, *88* : 2, p. 189-191.

GRUESSNER, A.; SCHNIDER, O.: Anticough agents comprising (+)-3-hydroxy-N-methylmorphinan ethers. *British Patent* No. 713146, 4 August 1954.

H

HENECKA, H.: Neue Synthesen in der Morphinanreihe (New syntheses in the morphinan series). *Justus Liebig's Annalen der Chemie*, 1953, *583* : 2, p. 110-128.

HOFFMANN-LA ROCHE & CO.: Morphinan derivatives and salts thereof. *British Patent* No. 685634, 7 January 1953.

———; ———: Isoquinoline derivatives. *British Patents* No. 685748,—749,—750, 7 January 1953.

K

KAYSER, F.: Konstitution und Synthese des Morphins (Constitution and synthesis of morphine). Part I* *Chemiker Zeitung*, 1953, 77 : 19, p. 645-648; Part II. *Ibid.*, 1954, *78* : 2, p. 37-41.

KUMMER, A.: Praktische Erfahrungen mit einem neuen Hustenmittel Romilar Roche. (Practical experience with a new cough medicine Romilar Roche). *Praxis*, 1955, *44* : 6, p. 132.

L

LANDMESSER, C. M; FORMEL, P. F.; CONVERSE, J. G.: Comparative effects of a new narcotic antagonist (levallorphan tartrate) upon the respiratory responses to carbon dioxide during narcotic and barbiturate

depression in anesthetized man. *Anesthesiology*, 1955, *16* : 4, p. 520-535.

LOEFFLER, A.; GINSBURG, D.: Open-chain analogs of morphine. *Journal of the American chemical society*, 1954, *76*, p. 3731-3732.

M

MALORNY, G.: Zur Wirkungsweie spezifischer Morphinantagonisten 1. Die Beeinflussung der zentralerregenden Wirkung von Morphinverwandten und N-Methylmorphinan-Derivaten bei der Maus (Mode of action of specific morphine antagonists. 1. Influence on the central stimulating effect of morphine and N-methylmorphinan in mice). *Arzneimittel-Forschung*, 1955, 5 : 5, p. 252-259.

MALORNY, G.; OHNESORGE, F. K.: Zur Wirkungsweise synthetischer Morphinanderivate (Mode of action of synthetic morphinan derivatives). *N. Sch. Archiv für Experimentelle Pathologie und Pharmakologie*, 1955, *224* : 5-6, p. 81-82.

MAURER, H.: Die hustenstillende Wirkung von Verbindungen der Dromoranreihe (Cough controlling effect of compounds of the dromoran series. Effet de contrôle de la toux de certaines préparations de la série du Dromoran). *Deutsche medizinische Wochenschrift*, 1955, 80 : 10, p. 351-353.

MAY, E. L.; MURPHY, J. G.: Structures related to morphine. Synthesis of an analog of N-methylmorphinan. *American chemical society* (Abstracts), 126th meeting, 12-17 Sept. 1954, p. 18N-19N.

MAYER, W.: Klinische Erfahrungen mit dem neuen synthetischen Analgeticum Citarin Bayer (Clinical experiences with the new synthetic analgesic Citarin produced by Bayer). *Medizinische Monatsschrift*, 1955, *9* : 5, p. 319-320.

MURPHY, J. G.; MAY, E. L.: Structures related to morphine. I. 2-(2-dimethyl-aminoethyl)-2-phenylcyclohexanone and derivatives. *Journal of organic chemistry*, 1954, *19*, p. 615-617; II. An isomer of N-methylmorphinan. (E. L. MAY; J. G. MURPHY) *Ibid.*, p. 618-622.

P

PELLMONT, B.: The influence of different drugs on the analgesic activity of Levorphan. *Journal of pharmacology and experimental therapeutics*, 1954, *110* : 1, p. 42 (abstract).

PITTINGER, C.B.; GROSS, E.G.; RICHARDSON, O. M: The effect of nalorphine levallorphan and analogues of levallorphan upon the hyperglycemic response of dogs to levorphan. *Journal of pharmacology and experimental therapeutics*, 1955, *114* : 4, p. 439-444.

PITRE, D.: Una nuova sintesi della morfina (New synthesis of morphine). *Il Farmaco*, 1954, 9 : 3, p. 183-186.

Q

QUAGLIA, C.; FRANCO, L. G.: Il l-idrossi-N-metilmorfinano, analgesico di sintesi, nei dolori da processi neoplastici (The synthetic analgesic agent l-hydroxy-N-methylmorphinan in the control of pain caused by neoplastic processes. *Gazetta medica italiana*, 1954, *113* : 10, p. 297-301.

R

RADNAY, P. A.; HECHTER, R. H.: Effect of l-allorphan tartrate on respiratory depression during nitrous oxide-oxygen anesthesia supplemented by l-Dromoran tartrate. *Journal of the international college of surgeons*, 1955, *23*, p. 38-50.

RANDALL, L. O.; KRUGER, J.; CONROY, C.; KAPPELL, B.; RENSON, W. M: Peripheral effects of the optical antipodes of 3-hydroxy-N-methyl-Morphinan and some of their derivatives. *N.-Schm. Archiv für experimentelle Pathologie und Pharmakologie*, 1953, *220* : 1-2, p. 26-39.

S

SANTARATO, R.: Azione dei farmaci sul metabolismo del piruvato nei feti e negli animali giovani. II. Morfina e morfinosimili di sintesi (Effect of drugs on the metabolism of pyruvate in fetuses and young animals. II. Morphine and synthetic morphine-like drugs). *Bollettino della società italiana di biologia sperimentale*, 1953, *29* : 4, p. 628-630.

SCHALLEK, W.; WALZ, D.: Cardiovascular and central nervous system effects of the morphinan series (21344). *Proceedings of the society for experimental biology and medicine*, 1954, *87* : 1, p. 233-236.

SCHNIDER, O.; GRUESSNER, A. (Hoffmann-La Roche Inc.) : Optically active 3-methoxy-N-methylmorphinans and their salts. United States Patent No. 2,676,177, 20 April 1954.

SCHNIDER, O.; BROSSI, A.; VOGLER, K.: (Hydroxymorphinan. V. Optically active benzyloctohydroisoquinolines). *Helvetia chimica acta*, 1954, *37*, p. 710-720.

SHORE, P. A.; AXELROD, J.; HOGBEN, C. A. M.; BRODIE, B. B.: Observations on the fate of dromoran in the dog and its secretion into the gastric juice. *Journal of pharmacology and experimental therapeutics*, 1955, *113* : 2, p. 192-199.

T

THOMAS, D. V.; TENNEY, S. M.: Effect of levorphan and levallorphan on the respiratory mechanism of normal man. *Journal of pharmacology and experimental therapeutics*, 1955, *113* : 3, p. 250-255.

TUENNERHOFF, F. K.; SCHWABE, H. K.: Untersuchungen zur Frage der Verwendbarkeit synthetischer Methoxy-methyl-morphinane; Beitrag zur Therapie der verschiedenen Hustenformen bei Lungentuberkulose (Possible use of synthetic 3-methoxy-N-methylmorphinan; contribution to the therapy of the various types of cough in pulmonary tuberculosis). *Klinische Wochenschrift*, 1955, *33* :23-24, p. 576-580.

V

VIDIC, E.: Nachweis und quantitative Bestimmung des Dromoran sowie seine Unterscheidung von anderen stark wirkenden Analgetica in biologischem Material (Detection and quantitative determination of dromoran as well as its differentiation from other analgesics with powerful effect in biological material). *Arzneimittel-Forschung*, 1953, *3* : 8, p. 428-435.

Y

YOUNG, D.C.; PLOEG, R. A. V.; FEATHERSTONE, R. M.; GROSS, E. G.: The interrelationships among the central, peripheral and anticholinesterase effects of some morphinan derivatives. *Journal of pharmacology and experimental therapeutics*, 1955, *114* : 1, p. 33-37.

Z

ZINDLER, M.; GANZ, P.: Ein Antidot der Opiate; die antagonistische Wirkung von (-)3-Oxy-N-allyl-morphinan (Ro 1-7700) auf die Atemdepression nach hohen Dosen von Morphin und Morphin-Abkömmlingen (An antidote against opiates; the antagonistic effect of (-) hydroxy-N-allylmorphinan (Ro-1-7700) on respiratory depression after high doses of morphine and morphine derivatives). *Deutsche medizinische Wochenschrift*, 1955, *80* : 12, p. 410-412.

E. Dithienylbutenylamines and miscellaneous syntheties

E

EDDY, N. B.; LEIMBACH, D.: Synthetic analgesics II. Dithienylbutenyl- and dithienylbutylamines. *Journal of pharmacology and experimental therapeutics*, 1953, *107* : 3, p. 385-393.

F

FLINTAN, P.; KEELE, C. A.: Clinical trial of some analgesic dithienylalkanylamines (abstract). *Journal of pharmacology and experimental therapeutics*, 1954, *110* : 1, p. 18.

———; ———: Analgesic and other actions of some dithienylbutenyl-amine compounds in man. *British Journal of pharmacology*, 1954, *9* :1, p. 106-117.

G

GREEN, A. F.: Analgesic and other properties of 3 : 3-Dithienylalkenylamines. *British journal of pharmacology and chemotherapy*, 1953, *8* : 1, p. 2-9.

I

ISBELL, H.; FRASER, H. F.: Actions and addiction liability of the dithienylbutenylamines in man. *Journal of pharmacology and experimental therapeutics*, 1953, *109* : 4, p. 417-421.

S

SUGIMOTO, Norio; SAITO, Seiichi; OSHIRO, Susumu : Synthetic analgesics. IV. Synthesis of 1,1-di(2-thienyl)-2-methyl-3- (tertiary-amino) propenes. *Journal of the Pharmaceutical society of Japan*, 1953, *73*, p. 1381-1383.